Towards the Synthesis of Batrachotoxin-Formation of Alkynyl Stannanes

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Summary: Batrachotoxin, isolated from frogs belonging to the genus Phyllobates, is a very potent neurotoxin and a steroidal alkaloid that has been found to block the Na+ channels in nerves and muscles resulting in arrhythmias or cardiac arrest leading to death. Research on this toxin is limited due to difficult isolation but many attempts have been made towards its total and partial synthesis. The present work indicates our efforts towards the formation of steroidal skeleton of this neurotoxin in high/improved yield by employing radical mediated cyclization which led to many interesting results. The successful model study towards the formation of the steroidal skeleton is also reported here.

Keywords: Batrachotoxin, radical mediated reaction, Bu3SnH, AIBN, alkynyl stannanes.

Introduction

The famous neurotoxin batrachotoxin 1 is a member of a family of steroidal alkaloids called batrachotoxins. The structure of 1 includes a steroid skeleton and an oxazepane ring.[1] The batrachotoxin family includes batrachotoxin 1, homo-batrachotoxins 2, batrachotoxinin-A 3 and pseudobatrachotoxin (unstable, converts to batrachotoxinin-A 3 on standing).[2] These toxins were first discovered in poison dart frogs of the genus Phyllobates [3] and were used to poison the arrows for killing animals.

Batrachotoxin 1 tends to affect the nervous system by causing the irreversible opening of Na+ channels in the nerves causing a change in ion selectivity of the ion channel by increasing the permeability of the channel toward larger cations, which results in depolarization of nerves leading to failure of nerve impulse transmission.[4] The persistent lack of nerve transmission to the muscles result in paralysis followed by death of an organism. The interesting feature about this neurotoxin is that it is in fact a cardio-toxin and causes heart arrest by interfering with heart conduction. This toxin has maximum activity at 37°C which is the body temperature of human beings so it is quite difficult to cure a person affected with this noxious and deadly chemical.[5]

Much research is required to better understand the mechanism of action of this toxin and its remedies. One aspect of this toxin is that if its action is controlled it can be used as an effective pain killer. The problem with research on this steroidal alkaloid is the difficult isolation from frogs since the amount being obtained is very small and the toxin is not much stable as well to be stored for much longer. Therefore different attempts have been made and are still in progress towards the total and partial synthesis of 1. The Imhof et al., carried out the first partial synthesis of batrachotoxinin A 1 starting form (+)-progesterone.[6, 7] The partial syntheses by Keana et al.[8] and Hudson et al.[9] are noteworthy approaches towards the partial syntheses of this complex steroidal alkaloid 1. Michio et al., carried out first total synthesis of batrachotoxinin A from Wieland-Miescher ketone by utilizing intramolecular furan Diels-Alder reaction and oxy-Michael reaction.[10] The work presented here is a reflection of our strategy towards the synthesis of steroidal skeleton of batrachotoxin 1 by the application of radical mediated cascade cyclization.

Results and Discussion

The presented work highlights the attempts towards the synthesis of steroidal backbone of batrachotoxin 1. The steroidal precursor 5 is of high concern to us, which was planned to be synthesized
by intermolecular radical mediated cascade cyclization of acetal 6 with cyclopentenone. We were expecting the five-membered C-ring formation of steroidal structure of 1 since exocyclic free radical is more stable than endocyclic.[11] The Pd-assisted intermolecular cascade cyclization of reduced derivative of acetal 6 also favoured five-membered C-ring in a separate study in our group.[12] The dihydroxylation of the steroidal precursor 5 followed by C-ring cleavage with Pb(OAc) 4 and condensation of resulting trione would furnish the complete synthesis of steroidal backbone 4 of 1 (scheme-1).

Model Study

We were interested to study the intermolecular radical mediated cascade cyclization on a model prior to complete synthesis of steroidal precursor 5. Hence addition of Br 2 to cyclohexenone 8 followed by dehydrohalogantion, involving E1cB mechanism, afforded enone 9 that upon direct addition of lithium phenylacetylide yielded propargylic alcohol 10. The deprotonation of 10 with NaH in DMSO followed by methylation with MeI afforded ether 11. The generation of n-Bu3Sn radical followed by intermolecular cascade cyclization of this ether 13 in the presence of 8 afforded an expected racemic enone 12 (scheme-2).

The abstraction of Br by n-Bu3Sn radical from ether 11 followed by conjugate addition of resulting vinyl radical 13 to enone 8 results an enol radical that upon addition to C≡C furnishes a radical 14. This radical is quenched with n-Bu3SnH resulting in β,γ-unsaturated enone 15 that upon isomerization results in the formation of more stable α,β-unsaturated enone 12 (scheme-3). The disappearance of sp-C's at 86.8 and 88.4 ppm and the presence of a carbonyl C, five CHs (four in aromatic and one in aliphatic region), seven CH2s in aliphatic region and a CH 3 in broad band (BB) and DEPT-assignments confirmed the formation of 12.

Synthesis of precursor 6

The Wieland-Miescher ketone (WMK) 18 was synthesized following the reported procedure in 76% ee.[13] The hydrogenation-cum-protection of enone 18 was carried out under H2 atmosphere in the presence of Pd[0] (5% on C), (CH3OH)2, catalytic amount of PdCl 2 (generates a small quantity of HCl that catalyses the reaction by oxidative addition of H2 to PdCl 2 followed by two successive reductive eliminations of HCl molecules) in MeOH afforded ketone 7 in good yield along with another isomer.[9] Different sequences were tried for the synthesis of enone 17a (scheme-4, Table-1).

Scheme-1: Reterosynthetic analysis of batrachotoxin 1.

Scheme-2: Model synthesis of steroid (A-des-C-nor-D-homosteroid 12).
Scheme 3: Mechanism of formation of model steroid 12 synthesized by refluxing 11 with cyclohex-2-ene, AIBN and n-Bu3SnH in PhH for 14 h (69%).

Scheme 4: Different strategies involving the generation of unsaturation next to carbonyl in 7.

Table 1: Synthesis of 7 under different conditions via scheme 4.

<table>
<thead>
<tr>
<th></th>
<th>a Product (Yield)</th>
<th>b Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA, Br2, THF, –78°C → rt</td>
<td>16a (62) NaOAc, MeOH, reflux (12 h)</td>
<td>16a (16)</td>
</tr>
<tr>
<td></td>
<td>LiCl, MeOH, reflux (10 h)</td>
<td>16a (16)</td>
</tr>
<tr>
<td></td>
<td>2,4,6-Collidine, MeCN, reflux (18 h)</td>
<td>16a (16)</td>
</tr>
<tr>
<td>LDA (-78°C), PhSeCl, THF, –78°C → rt</td>
<td>16b (77) H2O2, EtOAc, 0°C (1.5 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>H2O2, EtOAc, cyclohexene, 0°C (2 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>H2O2, CH2Cl2, cyclohexene, pyridine, 0°C (2 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>H2O2, CH2Cl2, cyclohexene, Et2N, 0°C (2 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>H2O2, NaOH, NaHCO3, cyclohexene, Et2N, MeOH, 20°C (20 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>m-CPBA, CH2Cl2, –78°C → rt (20 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td>LDA (-78°C), (PhS)2, THF, –78°C → rt</td>
<td>16c (71) i) NaIO4, MeOH/H2O (2.5:1), 0°C → rt (20 h); ii) CaCO3, PhMe, reflux (20 h)</td>
<td>16c (18), 17b (8)</td>
</tr>
<tr>
<td></td>
<td>i) NaIO4, cyclohexene, MeOH/H2O (2.5:1), 0°C → rt (20 h); ii) CaCO3, PhMe, reflux (20 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>i) m-CPBA, CH2Cl2, –78°C → rt (20 h); ii) CaCO3, PhMe, reflux (20 h)</td>
<td>17a (17)</td>
</tr>
<tr>
<td></td>
<td>i) NaIO4, cyclohexene, MeOH/H2O (2.5:1), 0°C → rt (20 h); ii) CaCO3, PhMe, reflux (20 h)</td>
<td>16c (23), 17c (20)</td>
</tr>
<tr>
<td>LDA (-78°C), N-tert-butylphenylsulphinimidoyl chloride, -78°C (1h)</td>
<td>16d (79) n-BuOLi (1.2 eq), THF, –78°C → rt</td>
<td>16d (16)</td>
</tr>
<tr>
<td></td>
<td>n-BuOLi (2.4 eq), THF, –78°C → rt</td>
<td>16d (16)</td>
</tr>
<tr>
<td></td>
<td>LDA (2.4 eq), THF, –78°C → rt</td>
<td>16d (16)</td>
</tr>
<tr>
<td></td>
<td>NaH (2.4 eq), MeCN, 0°C → rt</td>
<td>16d (16)</td>
</tr>
<tr>
<td>LDA (-78°C), TESOTf, Et3N, THF, –78°C → rt (over night)</td>
<td>16e (67) DDQ (2 eq), HMDS (2 eq), dry PhH, rt, over night</td>
<td>17a (41)</td>
</tr>
<tr>
<td></td>
<td>DDQ (2 eq), HMDS (3 eq), dry PhH, rt, over night</td>
<td>17a (41)</td>
</tr>
<tr>
<td></td>
<td>DDQ (2 eq), HMDS (3 eq), dry PhH, rt, over night</td>
<td>17a (41)</td>
</tr>
<tr>
<td></td>
<td>DDQ (4 eq), HMDS (4 eq), dry PhH, rt, over night</td>
<td>16e (15), 17a (59)</td>
</tr>
<tr>
<td></td>
<td>DDQ (4 eq), HMDS (4 eq), dry PhH, rt, over night</td>
<td>17a (51)</td>
</tr>
<tr>
<td></td>
<td>DDQ (4 eq), HMDS (4 eq), dry PhH, rt, over night</td>
<td>17a (51)</td>
</tr>
<tr>
<td></td>
<td>DDQ (8 eq), HMDS (4 eq), dry PhH, rt, over night</td>
<td>17a (36)</td>
</tr>
</tbody>
</table>

*Traces of 18e were also isolated.
The formation of silyl enol ether 16e followed by oxidation with DDQ and HMDS (2:3) provided the best yield of enone 17a. The addition of Br₂ to enone 17a followed by dehydrohalogenation, involving E₁cB mechanism, afforded α-bromo enone 19 (the immediate use of this compound in the next reaction is strongly recommended since it tends to decompose upon standing even at low temperature in dark and dry conditions). The presence of only one olefinic proton in ¹H-NMR indicated the substitution at olefine centre in 7 and appearance of two [M+H] signals at 303.0432 and 301.0452 amu (1:1) confirmed the presence of Br in enone 19. The generation of lithium trimethylsilylacetylide from TMS-acetylene by reacting with LDA at –78ºC followed by addition as drops to a solution of enone 19 (–78ºC) afforded the alcohol 20 in acceptable yield. The strong absorbance of O-H at 3391 cm⁻¹, the appearance of two sp-quaternary Cs at 67.3 and 90.8 ppm and 9H integral signal of Si(CH₃)₃ at 0.00 ppm confirmed the synthesis of alcohol 20 (scheme-5).

The transacetalization of 20 with catalytic amount of p-TSA afforded acetal 21 in good yield (this led to complete the C3-C9 acetal linkage of batrachotoxin 1). The disappearance of O-H absorbance in IR spectrum and two sets of doublet of four protons (3.72 and 3.78 ppm) of dioxydine ring and appearance of an additional singlet of OMe (3.32 ppm) confirmed the formation of acetal 21. The ring A of acetal 20 exists in boat conformation to facilitate transacetalization (scheme 6).

The desilylation of acetal 21 with TBAF (THF/H₂O 9:1, 0ºC) afforded the required synthon 6 in excellent yield. The formation of 6 was confirmed by the disappearance of nine ¹Hs of TMS-moiety at 0.00 ppm and the appearance of a sp-hybridized CH at 75.5 ppm in ¹³C-NMR broad band (BB) and DEPT-assignments. The synthesis of acetal 6 is an important milestone that can lead to the synthesis of steroidal precursor 5 by radical mediated intermolecular cascade cyclization.

Radical Mediated Cyclization of 6

The enone 5 is a C-nor steroid that may be extended to six membered by dihydroxylation with OsO₄ followed by ring cleavage with Pb(OAc)₄, which upon intramolecular condensation of resulting trione shall afford 4. The reduction of 6 under H₂ atmosphere, using Lindlar’s catalyst, followed by Pd-assisted cascade cyclization in microwave (MW) environment afforded 5 in 45% yield (scheme 7).[12] That’s why we tried an alternate method to improve the yield of enone 5.

![Scheme-5: Synthesis of precursor 6 (propargylic alcohol).](image)

![Scheme-6: Mechanism of transacetalization of 20.](image)
Scheme-7: Mechanism of formation of ethynyl stannane 22 synthesized by refluxing 6 with cyclopent-2-ene, AIBN and n-Bu3SnH in PhH for 14 h (15%).

The acetal 6 was subjected to intermolecular radical cyclization with n-Bu3SnH in the presence of AIBN as radical initiator. The solution of n-Bu3SnH was added as drops over three hours to the stirred solution of acetal 6, AIBN and cyclopent-2-enone in refluxing benzene. After heating under reflux for a further 14 hours a mixture of inseparable compounds (40%), starting material (45% recovery) and an unknown compound 22 (15%) was obtained. The 1H-NMR indicated the presence of n-Bu3Sn group, OMe and only one 1H in the olefinic region. The singlet of acetylenic proton at 2.50 ppm disappeared and the integration of high field region showed the presence of cyclopentyl group. The presence C=O at 204 ppm confirms the presence of cyclopentyl group at C4 of acetal 22. Both the sp-carbons of acetylene appeared as quaternary carbons. All these evidences from 13C NMR suggest the substitution of acetylenic proton with n-Bu3Sn.

We think that the abstraction of bromine from 6 by n-Bu3Sn radical generates the vinyl radical 23a that undergoes conjugate addition to cyclopent-2-enone. The resulting radical 23b rather undergoing intramolecular cascade cyclization, by the participation of ethynyl group in close vicinity, abstracts acetylenic H leaving alkynyl radical 23c that is quenched by n-Bu3Sn radical to complete the substitution of Br by 3-ketocyclopentyl group (scheme-7). The addition of n-Bu3Sn radical to an alkyne is well known [15] but the substitution of acetylenic hydrogen with same radical is not available in literature.

The change of free radical source, solvent, mode of free radical generation (thermolytic or photolytic) and reflux time improved nothing (Table-2). After the failure of desired intermolecular cascade cyclization by n-Bu3SnH and (BzO), we decided to generate n-Bu3Sn radical slowly in situ by the reaction of Na(CN)BH3 with n-Bu3SnCl at elevated temperature.[16] By bearing in mind the low reactivity of Na(CN)BH3, we added it’s solution slowly in refluxing t-BuOH to the stirred solution of acetal 6, cyclopent-2-enone, n-Bu3SnCl and AIBN.

We were delighted to see the total disappearance of the starting material to form only one compound 24 that was invisible under UV light and appeared after treatment with KMnO4 solution. The NMR showed the presence of n-Bu3Sn group in the molecule and four protons in olefinic region. The two AB type dd at 5.62 and 5.67 ppm showed the normal coupling constants (10.2, 1.8 and 10.5, 3.6 Hz respectively) as we observed in 6 & 21; this confirms the presence of vinyl bromide in the molecule. The two other doublets at 5.88 and 6.24 ppm exhibited the large coupling constants (19.5 Hz in both cases). It indicates the presence of an olefin with trans geometry of the coupling protons. This evidence indicates that this olefin is isolated and surrounded by quaternary carbon atoms. The other information that 1H-NMR revealed is the disappearance of the acetylenic 1H (2.5 ppm) of acetal 6.

Table-2: Radical mediated cyclization of 6 with cyclopent-2-enone under following conditions.

<table>
<thead>
<tr>
<th>Free Radical Initiator</th>
<th>Mode</th>
<th>Solvent±</th>
<th>Time (h)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 AIBN, n-Bu3SnH</td>
<td>∆</td>
<td>PhH</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>2 (BzO)2</td>
<td>∆</td>
<td>PhH</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>3 (BzO)2</td>
<td>∆</td>
<td>PhMe</td>
<td>06</td>
<td>-</td>
</tr>
<tr>
<td>4 (BzO)2</td>
<td>hv*</td>
<td>Et2O</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>5 AIBN, Na(CN)BH3, n-Bu3SnCl</td>
<td>∆*+</td>
<td>t-BuOH</td>
<td>20</td>
<td>24 25</td>
</tr>
<tr>
<td>6 AIBN, Na(CN)BH3, n-Bu3SnCl</td>
<td>∆*+</td>
<td>t-BuOH</td>
<td>20</td>
<td>24 25</td>
</tr>
</tbody>
</table>

±refluxing condition, *150 W W-lamp, **high concentration (0.04 M) of 6, ²low concentration (0.02 M) of 6.
The $^{13}$C-NMR indicated the presence of four CHs and two quaternary carbons in the olefinic region, two quaternary $sp$ carbons, three CH$_2$s and one CH$_3$ of the butyl chain of $n$-Bu$_3$Sn group. The rest of the $^{13}$C spectra were in resemblance with that of the starting material 6. No additional methylene and carbonyl carbons corresponding to those of cyclopentenone were observed that indicates no 1,4-Michael addition of vinyl radical 23a to cyclopent-2-enone had taken place. This information led us in elucidating the structure of 24. We think that the vinyl radical 23a adds to the C=C of another acetal 6 to form another vinyl radical. This coupled vinyl radical 24a further undergoes H-abstraction from the $sp$ carbon to generate ethynyl radical 24b that is quenched with $n$-Bu$_3$Sn radical to form diketal 24 (scheme-8).

The concentration of the acetal 6 and cyclopentenone would be the reason of this failure. It seems to be most likely that an increase in the number of equivalents of cyclopentenone and dilution of the acetal 6 may lead the reaction towards desired direction. In this hope we carried out the reaction under same conditions with six equivalents of cyclopentenone and dilution to double volume and got different results. The TLC analysis showed the formation of two products. The upper component was diacetal 24 as major product. The lower TLC component 25 showed some surprising $^1$H and $^{13}$C-NMR data. The $^1$H-NMR showed the absence of $n$-Bu$_3$Sn group and the presence of acetylenic proton, methoxy and two protons in olefinic region. The olefinic protons showed one dd at 5.64 ppm with cis coupling constants (8.4, 4.2 Hz) and an unresolved broad doublet with small (cis) coupling constants (9.3 Hz). The $^{13}$C-NMR showed resemblance to the characteristic signals of the starting material 6. In addition to these $^{13}$C signals we observed two other CHs in olefinic region at 125.9 and 131.5 ppm. These evidences indicate the formation of reduced acetal 25. This seems to be resulted by the generation of vinyl radical 23a followed by quenching with $n$-Bu$_3$SnH (scheme-9).

Scheme-8: Mechanism of formation of ethynyl stannane 24 synthesized by refluxing 6 with cyclopent-2-ene, AIBN, $n$-Bu$_3$SnCl and Na(CN)BH$_3$ in t-BuOH for 20 h (35%).

Scheme-9: Mechanism of free radical mediated reduction of bromoacetal 6 synthesized by refluxing 6 with cyclopent-2-ene, AIBN, $n$-Bu$_3$SnCl and Na(CN)BH$_3$ in t-BuOH for 24 h (23%).
By this transformation it looks that the dilution worked up to somehow, whereas the failure of coupling of cyclopent-2-enone with vinyl radical 23a is still not clear.

**Experimental**

The TLC was carried out on pre-coated silica gel (0.25 mm thick layer over Al sheet, Merck) with fluorescent indicator. The spots were visualized by this transformation it looks that the dilution worked up to somehow, whereas the failure of coupling of cyclopent-2-enone with vinyl radical 23a is still not clear.

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25.9 (q, Me at C1), 31.5, 31.6 (t, C9, 10), 37.2 (t, C7), 37.6 (t, C3), 42.5 (d, C6), 48.3 (s, C1), 64.0, 64.1 (t, CH2O), 109.2 (s, C8), 214.9 (s, C2); LREIMS (m/z): 224 [M + Na]+ (6%), 99 [2-ethenyl-1,3-dioxolane]+ (100%).

2-Bromocyclohex-2-enone (9)

A solution of Br2 (1.1 mL, 3.44 g, 21.2 mmol, 1.02 eq) in CH2Cl2 (15 mL) was added as drops to a well stirred and ice chilled solution of cyclohex-2-enone (2 mL, 2.0 g, 20.83 mmol, 1 eq) in CH2Cl2 (50 mL) and the resulting solution was stirred at 0°C for 1 hour followed by dropwise addition of Et3N (5 mL, 3.57 g, 35.4 mmol, 1.7 eq) at room temperature and the reaction mixture was stirred for 2 hours. The unreacted Et3N was quenched with dil. aq. HCI and washed consecutively with H2O and brine (25 mL each). The extraction of aq. layer with CH2Cl2 (3×25 mL), dryness over anhydrous Na2SO4, filtered and concentrated under reduced pressure to yield the alcohol as yellow oil (2.84 g, 90%). Rf: 0.63 (CHCl3/petrol 1:3); d: 0.97 g/mL; 1H-NMR δH: 1.83 (2H, t, J = 6.0 Hz, H5), 2.17 (2H, d, J = 5.8, 4.3, 1.5 Hz, H4), 2.23 (2H, ddd, J = –14.2, 7.1, 2.1 Hz, H6), 3.49 (3H, s, OCH3), 6.32 (1H, t, J = 4.2 Hz, H3), 7.30-7.40 (5H, m, Ph protons); 13C-NMR δC: 18.3 (t, C5), 27.8 (t, C4), 35.1 (t, C6), 51.9 (s, OMe), 75.0 (s, C1), 86.8 (s, C2), 88.4 (s, C1′), 124.4 (s, C1′), 126.3 (3×, d, C3′, C4′), 131.9 (2×, d, C2′, C3′), 131.7 (s, C2), 133.9 (d, C3); LREIMS (m/z): 290, 292 [M+] (8%), 275, 277 [M′-Me]+ (8%), 259, 261 [M′-OMe]+ (29%), 211 [M′-Br]+ (100%), 101 [PhC≡C=]+ (10%).

2-Bromo-1-(2-phenylethynyl)cyclohex-2-enol (10)

The -BuLi (6.6 mL of 1.7 M, 2.5 eq) was added as drops to a solution of i-Pr2NH (4.0 mL, 2.87 g, 28.4 mmol, 2.5 eq) in THF (25 mL) at –78°C, and the resulting solution was stirred at room temperature and stirred overnight. The reaction was quenched with sat. NH4Cl sol. (15 mL) and was extracted with CH2Cl2 (3×25 mL). The combined organic extract was dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to yield the crude ether as reddish yellow oil that upon column chromatography afforded the pure product 11 as green yellow oil (4.2 g, 66%) in 7th to 13th fraction of 100 mL each. Rf: 0.63 (CHCl3/petrol 1:3); d: 0.97 g/mL; 1H-NMR δH: 1.83 (2H, t, J = 6.0 Hz, H5), 2.17 (2H, d, J = 5.8, 4.3, 1.5 Hz, H4), 2.23 (2H, ddd, J = –14.2, 7.1, 2.1 Hz, H6), 3.49 (3H, s, OCH3), 6.32 (1H, t, J = 4.2 Hz, H3), 7.30-7.40 (5H, m, Ph protons); 13C-NMR δC: 18.3 (t, C5), 27.8 (t, C4), 35.1 (t, C6), 51.9 (s, OMe), 75.0 (s, C1), 86.8 (s, C2), 88.4 (s, C1′), 124.4 (s, C1′), 126.3 (3×, d, C3′, C4′), 131.9 (2×, d, C2′, C3′), 131.7 (s, C2), 133.9 (d, C3); LREIMS (m/z): 290, 292 [M+] (8%), 275, 277 [M′-Me]+ (8%), 259, 261 [M′-OMe]+ (29%), 211 [M′-Br]+ (100%), 101 [PhC≡C=]+ (10%).

9-Benzyl-8a-methoxy-2,3,4,4a,6,7,8,8a-octahydro-fluoren-1-one (12)

A solution of n-Bu3SnH (0.45 mL, 5.0 g, 1.71 mmol, 2 eq) and cyclohexenone (0.1 mL, 0.1 g, 0.98 mmol, 1.15 eq) in benzene (5mL) was added drop wise over a period of 1 hour via syringe pump to a refluxing solution of 2-bromo-1-(2-phenylethynyl)cyclohex-2-enyl methyl ether 11 (0.25 g, 0.856 mmol, 1.0 eq) and AIBN (0.015 g, 87 µmol, 0.1 eq) in benzene (10 mL) and resulting solution was refluxed under N2 for 14 hours. Upon the completion of reaction the benzene was evaporated and n-Bu3Sn salts were precipitated off by adding brine followed by addition of acetone. The salts were filtered off and combined, dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford the product as a pale yellow oil (0.18 g, 69.2%). Rf: 0.53 (EtOAc/petrol 1:1); d: 1.01 g/mL; 1H-NMR δH: 1.39 (4H, pentet, J = 7.5 Hz, H3, H7), 1.56 (2H, s, C1′), 127.1 (s, C2), 128.2 (d, C2″ or C3″), 128.6 (d, C4″), 131.9 (d, C2″ or C3″), 132.3 (d, C3); ESIMS [M+Na]+: 301.0017, 299.0039 (found in 1:1 ratio), 301.1639, 299.1660 (calc., 163 mmu diff.).
A solution of n-BuLi (2.14 mL of 2.5M in hexanes, 5.342 g, 53.5 mmol, 1.2 eq) was added as drops to a stirred solution of i-Pr₂NH (7.5 mL, 5.413 g, 53.5 mmol, 1.2 eq) in THF (120 mL) in a flame dried flask at –78°C. The reaction mixture was stirred for further 15 minutes followed by the addition of (1S,6R)-8,8-ethylenedioxy-1-methylbicyclo[4.4.0]decan-2-one (1.000 g, 4.46 mmol, 1.0 eq). The reaction mixture was stirred for further 20 minutes followed by the addition of Br₂ solution (0.3 mL, 1.2 eq) in THF (10 mL) at –78°C. The reaction mixture was gradually warmed to room temperature and stirred overnight. The reddish brown solution was partitioned between H₂O (25 mL) and Et₂O (3×50 mL), the combined organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo to afford yellowish oil (19.245 g). The crude oil was chromatographed over flash silica (25 cm in height) in a column (4.7 cm diameter) and elution with petrol, 5, 10, 15, 20, 25 and 30% Et₂O/petrol (6×0.2, 0.5 L) afforded white crystalline solid (0.839 g, 62%) in fraction 57th-83rd (20 mL each). A small portion of this solid was further crystallised from Et₂O/petrol for spectroscopic analysis. R₆: 0.54 (Et₂O/petrol 2:1), IR (ν₂max, cm⁻¹): 1698 (C=O, isolated), [α]D: –35.0 (c = 1.23, CHCl₃); ¹H-NMR δH: 1.16-1.27 (1H, m, H5α), 1.23 (3H, s, Me at C1), 1.31-1.43 (3H, m, H9α, H10α), 1.58 (1H, dd, J = –13.8, 13.8, 4.5 Hz, H7α), 1.13 (3H, s, Me at C1), 1.33 (2H, dd, J = 4.8, 2.4 Hz, H5), 1.34-1.45 (2H, m, H9α, H10α), 1.58 (1H, dd, J = –13.8, 13.8, 4.5 Hz, H9β), 2.00-2.05 (1H, m, H6), 2.11 (1H, dd, J = –13.5, 3.3, 3.3 Hz, H7β), 2.18 (2H, br. d, J = 10.5 Hz, H4α, H10β), 2.33-2.42 (1H, m, H4β), 3.77 (4H, dd, J = 7.8, 2.1 Hz, CH₂-O), 4.83 (1H, dd, J = 12.3, 6.6 Hz, H3); ¹³C-NMR δC: 26.8 (q, Me at C1), 27.9 (t, C10), 31.9 (t, C9), 33.4 (t, C7), 35.8 (t, C4), 37.6 (t, C5), 43.1 (d, C6), 50.0 (s, C1), 54.9 (d, C3), 64.6, 64.7 (t, CH₂O), 109.6 (s, C8), 204.9 (s, C2); LREIMS (m/z): 223 [M⁺-Br]⁺ (29%), 99 [2-ethynyl-1,3-dioxolane]⁻ (100%); ESIMS [M+H]⁺ (amu): 327.0390, 325.0414 (found), 325.0410 (calc., 0.4 mmu diff.).

(1S,6R)-8,8-Ethylenedioxy-1-methyl-3-phenylseleno bicyclo[4.4.0]decan-2-one (16b)

A solution of n-BuLi (8.6 mL of 2.5M in hexanes, 1.377 g, 21.4 mmol, 1.2 eq) was added

Uncorrected Proof
dropwise to a stirred solution of i-Pr₂NH (3.0 mL, 2.166 g, 21.4 mmol, 1.2 eq) in THF (50 mL) in a flame dried flask at -78°C and stirred for 20 minutes followed by the addition of (1S,6R)-8,8-ethylenedioxy-1-methylbicyclo[4.4.0]decan-2-one 7 (4,000 g, 17.8 mmol, 1.0 eq) in THF (20 mL). The reaction mixture was stirred for a further 45 minutes followed by the addition of solution of (PhS)₂ (4.283 g, 19.6 mmol, 1.1 eq) in THF (15 mL) at -78°C. The reaction mixture was gradually warmed to room temperature and stirred overnight. The yellowish green solution was partitioned between sat. aq. NH₄Cl (25 mL) and Et₂O (3×50 mL), the combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford yellowish oil (4.846 g). The crude oil was chromatographed over flash silica (16 cm in height) in a column (3.5 cm diameter) and elution with petrol, 10, 15, 20, 25% Et₂O/petrol (6×0.5 L) afforded pure compound (3.114 g, 79%) in fraction 27th-47th (50 mL each). Rf 0.49 (Et₂O/petrol 2:1), IR (υmax, cm⁻¹): 3277 (N-H), 1703 (C=O, isolated); ¹H-NMR δH: 1.34 (3H, s, Me at C1), 1.42-1.47 (3H, m, H3), 1.50-1.53 (4H, m, H7), 1.68 (1H, dd, J = -13.5, 4.2 Hz, H4α), 2.28-2.32 (3H, m, H4β, H5α, H6), 2.48 (1H, dd, J = -15.3, 10.1, 10.1 Hz, H5β), 3.83-3.88 (4H, m, CH₂O), 4.20 (1H, dd, J = -12.9, 6.6 Hz, H3), 7.17 (2H, dd, J = 7.8, 1.8 Hz, H2), 7.21 (1H, t, J = 7.0 Hz, H4'), 7.33 (2H, dd, J = 8.1, 1.5 Hz, H3'); In minor product the Me at C1 and H3 appeared at 1.24 (3H, s) and 4.01 (1H, dd, J = 8.4, 6.0 Hz) respectively; ¹³C-NMR δC: 22.8 (t, C10), 26.8 (t, C9), 26.9 (q, Me at C1), 32.1 (t, C7), 32.9 (t, C8), 38.2 (t, C5), 43.4 (d, C6), 49.6 (s, C1), 55.2 (d, C3), 64.5, 64.6 (t, CH₂O), 109.6 (s, C8), 127.7 (d, C4), 129.3 (d, C2), 133.0 (d, C7), 134.4 (s, C1'), 209.9 (s, C2); ¹³C-NMR δC: 15.6 (d, C3), 22.8 (m/z): 332 [M⁺] (59%), 223 [M⁺-PhS]⁻ (37%), 99 [2-vinyl-1,3-dioxolane]⁻ (37%); EIMS MS [M⁺Na⁺]⁺ (amu): 355.1313 (found), 355.1338 (calc., 2.5 mmu diff.).

(1S,6R)-3-(S-Chloro-S-t-butylaminophenylthio)-8,8-ethylenedioxy-1-methylbicyclo[4.4.0]decan-2-one (16d)

A solution of n-BuLi (3.8 mL of 2.5M in hexanes, 0.600 g, 9.36 mmol, 1.4 eq) was added as drops to a stirred solution of i-Pr₂NH (1.2 mL, 0.812 g, 8.03 mmol, 1.2 eq) in dry THF (30 mL) at ~78°C. The reaction mixture was stirred for 20 minutes followed by dropwise addition of a solution of (1S,6R)-8,8-ethylenedioxy-1-methylbicyclo[4.4.0]decan-2-one 7 (1,500 g, 6.69 mmol, 1 eq) in dry THF (15 mL). The reaction mixture was stirred for further 45 minutes to ensure the complete enolization. Then Et₃N (1.39 mL, 1.016 g, 10.03 mmol, 1.5 eq) and Et₃SiOTf (2.30 mL, 2.652 g, 10.03 mmol, 1.5 eq) were successively added and after 15 minutes the cooling bath was removed. The reaction mixture was stirred at room temperature for 2 hours, quenched with saturated NH₄Cl solution (20 mL) and extracted with Et₂O (3×30 mL). The organic extract was dried over anhydrous MgSO₄ and concentrated in vacuo to afford yellowish oil (3.653 g pinkish coloured impure product along with white crystalline solid. The crystals were removed by filtration with petrol and the filtrate was concentrated. This filtrate was chromatographed over neutral Al₂O₃ (13 cm in
height) in a column of 3.5 cm diameter, which afforded 16e as colourless oil (1.517 g, 67%) in fraction 12th-17th (50 mL each) by elution with petrol, 0.50 (Et2O/petrol, 1:4); IR (νmax cm⁻¹): 2954 (C=C, H), 2876 (C-H, saturated); 1H-NMR δH: 0.59 (6H, q, J = 7.8 Hz, CH2-Si), 0.90 [9H, t, J = 7.8 Hz, CH2(Si)], 1.04 (3H, s, Me at C1), 1.23 (1H, dd, J = 12.3, 4.5 Hz, H7α), 1.14-1.45, 1.72-1.88 (3H+2H, m, H5, H9, H11α), 1.64 (1H, d, J = −11.7 Hz, H7β), 1.70 (1H, br. d, J = −11.4 Hz, H6), 1.91 (1H, dd, J = 8.7, 4.5, 2.1 Hz, H4α), 1.97 (1H, dd, J = 6.3, 2.7 Hz, H10β), 2.04 (1H, ddd, J = −13.2, 3.9, 3.9 Hz, H4β), 3.87 (4H, s, CH2O), 4.51 (1H, dd, J = 3.9, 3.0 Hz, H3); 13C-NMR δC: 5.4 (3×, t, CH2-Si), 7.1 [3×, q, CH2(Si)], 28.2 (q, Me at C1), 21.4 (t, C10), 23.9 (t, C4), 32.3, 32.5 (t, C5, C9), 64.4, 64.6 (t, CH2O), 99.8 (d, C3), 110.2 (s, C8), 135.9 (s, C2); LREIMS (m/z): 338 [M + ]⁻, 224 [M+Et2SiCH=CH2]⁻ (47%), 115 [Et3Si]⁺ (38%), 99 [2-ethyl-1,3-dioxolane]⁻ (100%); ESIMS [M+Na]⁺ (amu): 361.2169 (found), 361.2137 (requires, 3.2 mmu diff.).

(IS,6R)-8,8-Ethylenedioxy-1-methylbicyclo[4.4.0]dec-3-en-2-one (17a)

Procedure A: A solution of H2O2 (1.9 mL of 35%aq. solution, 0.735 g, 21.6 mmol, 2 eq) was added as drops to a stirred solution of (IS,6R)-8,8-ethylenedioxy-1-methyl-3-phenylselenobicyclo[4.4.0]dec-2-one 16b (2.543 g, 78%) (Et2O/petrol, 1:1), IR (νmax cm⁻¹): 1730 (C=O, conjugated); [α]D: +42.4 (c = 1.04, CHCl3); 1H-NMR δH: 1.09 (3H, s, CH3 at C1), 1.22 (1H, ddd, J = −13.2, 13.2, 4.5 Hz, H7α), 1.36-1.44 (1H, m, H11α), 1.45-1.57 (2H, m, H9), 1.65 (1H, t, J = −13.2 Hz, H10β), 2.00 (1H, dd, J = −19.8, 5.7 Hz, H5α), 2.16 (1H, ddd, J = −13.2, 3.7, 4.2 Hz, H6), 2.26 (1H, ddd, J = −13.2, 3.3, 3.3 Hz, H7β), 2.72 (1H, dd, J = −19.8, 2.7, 2.7 Hz, H15β), 3.85 (4H, br. d, J = 2.4 Hz, CH2O), 5.85 (1H, dd, J = 10.2, 2.4 Hz, H3), 6.67 (1H, ddd, J = 9.9, 5.7, 2.4, 1.5 Hz, H4); 13C-NMR δC: 24.8 (q, Me at C1), 30.0 (t, C5), 31.7 (t, C7), 32.3 (t, C9), 38.1 (t, C10), 40.3 (d, C6), 46.1 (s, C1), 64.6 (2×, t, CH2O), 109.4 (s, C8), 128.2 (d, C3), 146.3 (d, C4), 203.2 (s, C2); LREIMS (m/z): 222 [M+Me]⁻ (53%), 207 [M+Me]⁻ (10%), 193 [M−H+CO]⁻ (33%), 99 [2-ethyl-1,3-dioxolane]⁻ (100%); ESIMS [M+Na]⁺ (amu): 245.1148 (found), 245.1142 (calc., 0.6 mmu diff.).

(S,6R)-1-Methylbicyclo[4.4.0]decane-2,8-dione (17b)
A flame-dried flask was charged with (1S,6R)-8,8-ethylenedioxy-1-methylbicyclo[4.4.0]decan-2-one (7.050 g, 22.3 mmol, 1.0 eq), o-iodoxybenzoic acid (IBX, 1.248 g, 4.46 mmol, 2.0 eq) and DMSO (20 mL). The reaction mixture was heated at 70°C for 20 hours under mild N2 pressure. The cooled reaction mixture was then partitioned between H2O (25 mL) and CH2Cl2 (3×30 mL). The combined organic layer was dried over anhydrous MgSO4, filtered and concentrated under reduced pressure to afford colourless oil (6.400 g). The chromatographic separation of the crude over flash silica (22 cm in height) in a column (1.7 cm diameter) afforded the crystalline compound 17b (187 mg, 69%) in fraction 35th–41st (20 mL each) and starting material (160 mg) in 23rd–30th fraction, after elution with petrol, 10, 15, 20 and 25 % Et2O/petrol (4×0.15, 0.4 L). Rf: 0.44 (Et2O), IR (νmax, cm−1): 1699 (C=O, br. s); [α]20D +1.8 (c = 1.12, CHCl3); 1H-NMR δH: 1.14 (3H, Me at C1), 2.11 (1H, dd, J = 5.4, 3.0 Hz, H10α), 1.32 (1H, dd, J = –14.1, 4.2 Hz, H5α), 1.74 (1H, dd, J = 9.6, 1.2 Hz, H4α), 1.75 (1H, dd, J = –19.2, 9.6 Hz, H4β), 1.84–1.90 (1H, m, H5β), 2.05–2.16 (3H, m, H3, H6), 2.18 (1H, dd, J = 3.9, 0.9 Hz, H9α), 2.22 (1H, dd, J = 6.3, 1.2 Hz, H7α), 2.30 (1H, dd, J = 9.6, 1.8 Hz, H10β), 2.36 (1H, dd, J = –14.7, 3.0 Hz, H9β), 2.39 (1H, dd, J = –15.0 Hz, H7β); 13C-NMR δC: 23.3 (t, C4), 24.3 (q, Me at C1), 27.0 (t, C5), 34.1 (t, C10), 37.9, 38.8 (t, C7, C9), 44.1 (t, C3), 46.4 (d, C6), 48.9 (s, C1), 211.8, 214.6 (s, C2, C8); ESIMS: [M + H]+. (10%), 122 [M+.-2CO]+. (32%).

Aqueous HClO4 solution (44.2 mL of 1M, 4.443 g, 44.2 mmol, 0.28 eq) was added dropwise with vigorous stirring to a stirred suspension of ((−)-proline (8.729 g, 75.8 mmol, 0.48 eq) and 2-methyl-2-(3′-oxobutyl)cyclohexane-1,3-dione (31.000 g, 158 mmol, 1 eq) in MeCN (200 mL). The reaction flask was wrapped up by Al foil and stirred for 48 hours at 80°C. The ice-cold reaction mixture was quenched with sat. aq. NaHCO3 (50 mL) and extracted with CHCl3 (3×30 mL). Drying the organic layer over anhydrous Na2SO4 followed by filtration and evaporation under reduced pressure to afford colourless oil (6.400 g). The crude over flash silica (22 cm in height) in a column (1.7 cm diameter) afforded the crystalline compound 17a (1.756 g, 7.90 mmol, 1.0 eq) in CCl4 (50 mL) and dropwise addition of the Br2 (0.5 mL, 1.515 g, 9.48 mmol, 1.2 eq) was carried out in CCl4 (30 mL) at 0°C. The pyridine (1.9 mL, 1.875 g, 23.70 mmol, 3.0 eq) was added at once to the reaction mixture when the colour of Br2 persisted. The reaction mixture was stirred for 3 hours and the resulting white precipitate was filtered and washed with Et2O (50 mL) under suction. The combined filtrate was washed with 10% aq. HCl, sat. aq. NaHCO3 and brine (50 mL each), the aqueous layers were extracted with Et2O and combined with other organic layers. These organic layers were dried over anhydrous MgSO4, filtered and concentrated under reduced pressure to yield reddish brown oil (3.488 g). The column chromatography of the crude over flash silica (30 cm in height) in a column (2 cm diameter) afforded pure compound (1S,6R)-3-bromo-8,8-ethylenedioxy-1-methylbicyclo[4.4.0]decan-2-one (31.000 g, 158 mmol, 1 eq) in petrol (4×0.8, 2.4 L). Rf: 0.58 (CH2Cl2 / Et2O 1:3), d (g/mL): 1.067; IR (νmax, cm−1): 2875 (C=O, conjugated), [α]31D +15.4 (c = 1.56, CHCl3); 1H-NMR (300 MHz, CDCl3, δ in ppm): 1.39 (3H, s, Me at C6), 1.64 (1H, ddd, J = –13.5, 4.5, 4.5 Hz, H5α), 2.03–2.08 (2H, m, H4α, 5β), 2.37–2.41 (5H, m, H4, H8, H9), 2.67 (2H, t, J = 6.3 Hz, H10), 5.79 (1H, d, J = 1.8 Hz, H2); 13C-NMR (75 MHz, CDCl3, δ in ppm): 23.3 (t, C7, C9, C10), 30.0 (t, C5), 31.2, 34.0 (t, C4, C8), 38.0 (t, C10), 51.0 (s, C6), 126.1 (d, C2), 166.4 (s, C1), 198.8 (s, C3), 211.5 (s, C7); LREIMS (m/z): 178 [M+] (31%), 150 [M−CO]+ (10%), 122 [M′−2CO]+ (32%).
A solution of n-BuLi (6.7 mL of 2.5M in hexane, 1.0674 g, 16.68 mmol, 2 eq) was added as drops to a stirred solution of trimethylsilylacetylene (2.4 mL, 1.6383 g, 16.68 mmol, 2 eq) in THF (50 mL) at -78°C. The reaction mixture was stirred for 30 minutes in a flame-dried flask. A solution of (1S,2R,6R)-3-bromo-8,8-ethylenedioxy-1-methyl-2-(trimethylsilyl)ethynylbicyclo[4.4.0]dec-3-en-2-ol (20) was added as drops to a reaction flask at -78°C, gradually increased the temperature to room temperature and stirred overnight. The reaction was quenched with sat. aq. NH₄Cl solution (30 mL), diluted with H₂O (50 mL), extracted with Et₂O (3×100 mL), dried over anhydrous MgSO₄ and concentration under reduced pressure afforded crude yellow oil (4.962 g). The chromatography of the crude over flash silica (25 cm in height) in a column (4.0 cm diameter) and elution with petrol, 5, 10, 15 and 20% Et₂O/petrol (2×0.3, 3×0.4 L respectively) afforded colourless gum in 25th-35th fraction (50 mL each). The crystallization from Et₂O/petrol yielded colourless crystals (1.316 g, 55%). Rf 0.60 (Et₂O/petrol 1:1); IR (max, cm⁻¹): 3391 (O-H), 2923 (C=O), 2147 (C≡C), 1719 (C=O), [α]D²⁰ −2.3 (c = 0.886, CHCl₃); 1H-NMR (CDCl₃) δ: 0.00 (9H, s, Si-CH₃), 1.11 (3H, s, Me at C1), 1.45 (1H, t, J = −13.2 Hz, H5α), 1.57-1.63 (4H, m, H6, H7, H10α), 1.92-2.08 (3H, m, H9, H10β), 2.42 (1H, m, H5β), 3.72 (2H, d, J = 5.1 Hz, CH₃O), 3.78 (2H, d, J = 4.8 Hz, CH₃O), 5.89 (1H, t, J = 3.9 Hz, H4); 13C-NMR δ: 0.0 (3×, s, Q-Si-C), 25.3 (q, Me at C1), 30.3 (2×, t, C5, C7), 32.1 (t, C10), 35.9 (d, C6), 36.1 (t, C9), 41.3 (s, C1), 63.8, 64.5 (t, CH₃O), 67.3 (s, C12), 90.8 (s, C11), 106.4 (s, C2), 109.4 (s, C8), 125.7 (s, C3), 129.9 (d, C4), LREIMS (m/z): 400, 398 [M⁺] (5%), 383, 381 [M⁺-HO]⁺ (26%), 382, 380 [M⁺-H₂O]⁻ (83%), 367, 365 [M⁺-H₂O-Me]⁻ (62%), 319 [M⁺-Br]⁻ (33%), 73 [Me₂Si]⁺ (94%); ESIMS [M⁺Na]⁺ (amu): 423.0807, 421.0827 (found in 1:1 ratio), 423.0785, 421.0805 (requires, 2.2 mmu diff.).

(1R,3R,7R,8S)-6-Bromo-1-methoxy-8-methyl-7-(trimethylsilyl)enynyl-11-oxatricyclo[5.3.1.0³,⁸]undec-5-ene (21)

A solution of p-TSA.H₂O (139 mg, 0.728 mmol, 0.1 eq) in MeOH (30 mL) was added as drops to a stirred solution of the (1S,2R,6R)-3-bromo-8,8-ethylenedioxy-1-methyl-2-(trimethylsilyl)ethynylbicyclo[4.4.0]dec-3-en-2-ol (20) (2.909 g, 7.28 mmol, 1.0 eq) in MeOH (120 mL) at room temperature (20°C) and stirred for 5 hours. The reddish solution was neutralized to the pale yellow solution with Et₃N (0.15 mL, 111 mg, 0.19 mmol, 0.15 eq). Evaporation of MeOH in vacuo followed by the partitioning between H₂O and Et₂O (3×50 mL) dryness over anhydrous MgSO₄ and concentration under reduced pressure afforded crude yellow oil (4.962 g). The short column chromatography over flash silica and elution with 15 and 20% Et₂O/petrol (0.2, 0.5 L respectively) afforded the required compound (2.387 g, 89%) as colourless gum. Crystallization from Et₂O/petrol (60-80°C) was unsuccessful but the product solidified when kept in freezer. Rf: 0.54 (EtOEt/petrol 1:2); IR (max, cm⁻¹): 2961 (C≡C-H), 1719 (C=O), [α]D²⁰ +9.2 (c = 1.19, CHCl₃); 1H-NMR (CDCl₃) δ: 0.19 (9H, s, CH₃-Si), 0.99 (3H, s, Me at C8), 1.51 (1H, d, J = −13.1, 1.1 Hz, H2β), 1.91 (1H, d, J = −18.3, 5.8, 2.0, 0.6 Hz, H4α), 1.95-1.97 (1H, m, H3), 1.99 (1H, d, J = −12.4, 3.6, 3.6 Hz, H9β), 2.23 (1H, d, J = −12.2, 11.7, 5.3, 0.5 Hz, H10β), 2.41 (1H, d, J = −18.2, 4.3, 2.2 Hz, H6β), 3.32 (3H, s, OCH₃), 6.09 (1H, d, J = 5.8, 2.2, 0.9 Hz, H5); 13C-NMR δ: −0.3 (q, CH₂-Si), 20.8 (q, Me at C8), 30.9 (t, C9), 32.0 (t, C10), 32.9 (d, C3), 33.2 (t, C4), 35.5 (t, C2), 35.7 (s, C8), 50.1 (q, CH₂-O), 80.0 (s, C13), 91.8 (s, C12), 98.5 (s, C1), 103.6 (s, C7), 126.2 (s, C6), 127.6 (d, C5), 150.3 (d, C4), LREIMS (m/z): 370, 368 [M⁺] (8%), 355, 353 [M⁺-Me]⁻ (4%), 289 [M⁺-Br]⁻ (14%), 73 [Me₂Si]⁺ (100%); ESIMS [M⁺Na]⁺ (amu): 393.0693, 391.0716 (found in 1:1 ratio), 393.0676, 391.0699 (calc., 1.7 mmu diff.).

(1R,3R,7R,8S)-1-Methoxy-8-methyl-6-(3'-oxocyclopentyl)-7-(tri-n-butylstannylethynyl)-1-oxatricyclo[5.3.1.0³,⁸]undec-5-ene (22)

A solution of n-BuSnH (0.68 mL, 0.663 g, 8.08 mmol, 8.0 eq) and cyclopent-2-ene (0.41 mL, 0.441 g, 1.515 mmol, 1.5 eq) in benzene (6 mL) was added as drops over 3 hours to a refluxing solution of (1R,3R,7R,8S)-6-bromo-7-ethynyl-1-methoxy-8-methyl-11-oxatricyclo[5.3.1.0³,⁸]undec-5-ene (6) (0.300 g, 1.01 mmol, 1.0 eq) and AIBN (17 mg, 0.101 mmol, 0.1 eq) in benzene (12 mL). The solution was heated to reflux for further 14 hours. The solvent was evaporated in vacuo and the reaction mixture was partitioned between brine (15 mL) and Et₂O (3×25 mL). The combined organic layer was dried over
anhydrous Na$_2$SO$_4$ and concentrated and under reduced pressure to afford greenish yellow oil (0.812 g). The crude oil was chromatographed over flash silica in a column (37×1.6 cm) and elution with petrol, 2.5, 5, 7.5 and 10% Et$_2$O/petrol (0.3 L each) afforded the title compound (48 mg, 15% in 43$^{nd}$-54$^{th}$ fraction of 20 mL each. R$_f$: 0.67 (Et$_2$O/petrol 1:1); $^1$H-NMR δH: 0.80 [9H, t, $J$ = 7.3 Hz, CH$_3$(Sn)], 0.90 (6H, t, $J$ = 7.5 Hz, H1’S), 1.26 (6H, p, $J$ = 7.3 Hz, H2’S), 1.50 (6H, p, $J$ = 7.8 Hz, H3’S), 0.94 (3H, s, Me at C8), 1.56-1.68 (9H, m, H2, H2′, H4’, H5’, H6, H7, H10), 1.79 (1H, t, $J$ = 11.7 Hz, H2B), 1.86 (1H, dd, $J$ = –17.3, 12.2 Hz, H4α), 1.91-1.96 (3H, m, H9, H1′), 2.23 (1H, ddd, $J$ = –12.1, 12.1, 4.8 Hz, H4B), 2.34 (1H, ddd, $J$ = –18.3, 2.1, 2.1 Hz, H3), 3.26 (3H, s, OCH$_3$), 6.00 (1H, ddd, $J$ = 5.7, 0.9, 0.9 Hz, H5); $^{13}$C-NMR δC: 11.6 (3×, t, C1′), 14.0 (3×, q, C4′), 30.6, 31.0 (2×, t, C9, C9′), 31.6 (2×, s, C8, C8′), 32.1 (2×, t, C4′, C4″), 35.6 (2×, d, C3, C3′), 37.5 (2×, t, C2, C2′), 50.0 (q, CH$_3$O), 68.5 (s, C13), 79.4 (3×, s, C7, C7′, C12), 97.9 (2×, s, C1, C1′), 126.3, 132.9 (2×, d, C5, C5′), 128.1 (d, C13′), 149.3 (d, C12′), 153.4, 154.0.

(1R,3R,7R,8S)-7-Ethynyl-1-methoxy-8-methyl-11-oxatricyclo[5.3.1.0$^{3,8}$]undec-5-ene (25)

A solution of n-Bu$_3$SnCl (0.14 mL, 0.165 g, 0.51 mmol, 1.0 eq) in t-BuOH (5 mL) was added as drops over 3 hours to a stirred suspension of (1R,3R,7R,8S)-6-bromo-7-ethylhex-1-methoxy-8-methyl-11-oxatricyclo[5.3.1.0$^{3,8}$]undec-5-ene (0.150 g, 0.51 mmol, 1.0 eq), cyclo pent-2-ene (0.26 mL, 0.249 g, 3.06 mmol, 6.0 eq), Na(CN)BH$_3$ (64 mg, 1.01 mmol, 2 eq) and AIBN (17 mg, 0.1 mmol, 0.2 eq) in t-BuOH (20 mL) at reflux. The reaction mixture was held under reflux for 24 hours. The solvent was evaporated on high vacuum and the resulting reaction mixture was partitioned between brine (15 mL) and Et$_2$O (3×25 mL). The organic layer was combined, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford greenerish yellow oil (0.326 g). The crude oil was chromatographed over flash silica in a column (36×2 cm) and elution with petrol, 2.5 and 5% Et$_2$O/petrol (2×0.25 L, 0.75 L) afforded the title compound (25 mg, 23%) in 52nd-50th fraction of 20 mL each. R$_f$: 0.42 (Et$_2$O/petrol 1:3); $^1$H-NMR δH: 0.88 (3H, s, Me at C8), 1.20 (1H, br. d, $J$ = 12.3 Hz, H9α), 1.28 (1H, dd, $J$ = –14.1, 6.9 Hz, H9β), 1.46 (1H, dd, $J$ = 6.3, 2.1 Hz, H10α), 1.57 (1H, ddd, $J$ = 7.8, 7.8, 3.0 Hz, H2α), 1.80 (1H, d, $J$ = –11.4 Hz, H4α), 1.85 (1H, br s, H3), 1.94 (1H, ddd, $J$ = –12.0, 3.0, 3.0 Hz, H2β), 2.13 (1H, ddd, $J$ = –12.6, 12.6, 4.5 Hz, H10β), 2.27 (1H, t, $J$ = –19.5 Hz, H4β), 2.40 (1H, s, H13), 3.24 (3H, s, OCH$_3$), 5.62-5.66 (1H, m, H5), 5.83 (1H, d, $J$ = 9.3 Hz, H6); $^{13}$C-NMR δC: 20.9 (q, Me at C8), 29.8 (t, C9), 30.1 (t, C2), 31.4 (t, C10), 32.4 (s, C8), 33.8 (d, C3), 37.0 (t, C4), 50.0 (q, CH$_3$O), 72.9 (d, C13), 74.7 (s, C12), 84.9 (s, C7), 97.8 (s, C1), 125.9 (d, C5), 131.5 (d, C6); ESIMS [M+Na]$^+$ (amu): 241.1211 (found), 241.1207 (calc., 0.4 mmu diff.).
Conclusions

The failure of the ethynyl system to undergo cyclization to afford the desired enone 5 and the substitution of the terminal ethynyl proton with n-Bu₃Sn group in almost all of cases was attributed to the presence of the terminal alkyne proton which tends to terminate the radical reaction. The successful model study towards the cyclization of des-A steroidal skeleton is consistent with this inference. It is therefore proposed that the use of substituted acetylenes will lead to successful synthesis of enone 5.

The formation of alkynyl stannanes (22 & 24) can be exploited in reactions similar to Stille coupling. The cis-reduction of alkynyl stannanes affords the subsequent alkenyl stannanes.[7] The transmetallation of alkenyl or alkynyl stannanes with organo-Pd compounds followed by the reductive elimination of Pd⁰ may lead to the formation of new C-C bond. Similarly the transmetallation of stannyl group to Pd will lead to a substrate that may serve as an effective substrate for intramolecular or intermolecular Pd-mediated cascade cyclization upon reaction with various aryl/vinyl halides.

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