A total synthesis of (+)-isolaurepan

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ABSTRACT

A versatile and efficient method for the enantioselective synthesis of 2,7-*cis*-disubstituted oxepane **1c**, (+)-isolaurepan, using oxidative resolution of a secondary alcohol and highly diastereoselective Et₃SiH/TMSOTf-promoted reductive cyclization of a hydroxy ketone is described.

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Seven-, eight- and nine-membered medium ring ethers are encountered as common structural motifs of many ladder ether marine toxins and simpler *Laurencia* acetogenin metabolites.[1] However, their synthesis is generally difficult via standard cyclization methodologies.[2] Nevertheless, the challenge in their efficient construction has led to the development of several strategies for their synthesis,[1,3] mainly in racemic form.

In view of the increasing number of biologically active marine natural products containing medium and large sized cyclic ether derivatives,[4] much attention has been focussed on efficient approaches towards these systems. (+)-Isolaurepinnacin **1a** and (+)-neoisoprelaurefucin **1b** (Fig. 1) containing a 2,7-disubstituted oxepane core unit were mainly isolated from the genus *Laurencia*, and have been synthetic targets of considerable interest. (+)-Isolaurepan **1c** is a fully saturated analogue of the core of **1a** and other chiral oxepane derivatives.[5]

Kotsuki et al. reported the first total synthesis of (+)-isolaurepan via cis-selective reduction mediated by triethylsilane/TiCl₄.[6] A few more groups have described its formal synthesis by different approaches.[7] Although there have been a number of reports on the stereoselective construction of racemic *cis*-2,7-disubstituted oxepanes, literature describing synthetic strategies for its non racemic derivatives is rather scarce. Thus, a general strategy for the enantioselective synthesis of the functionalized medium ring ether skeleton present in many *Laurencia* non-terpenoid metabolites is highly desirable.
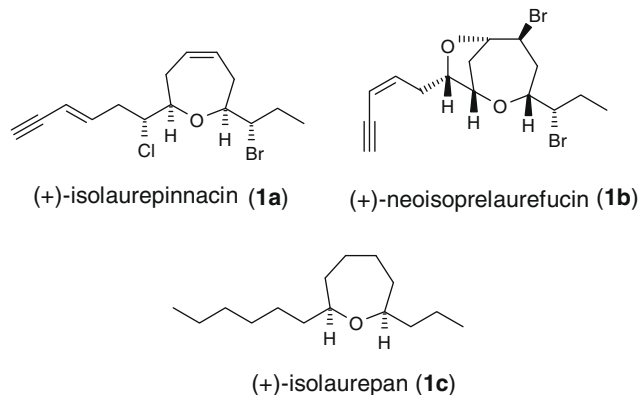

Figure 1. Structures of various 2,7-*cis*-disubstituted oxepanes.

As part of our research on the asymmetric synthesis of bioactive molecules,[8] we became interested in developing a general route to an intermediate which could be useful in the synthesis of a wide variety of functionalized non-racemic 2,7-*cis*-disubstituted cyclic ether-based molecules. Herein, we report the synthesis of (+)-isolaurepan (**1c**) starting from 1,6-hexanediol using oxidative resolution of a secondary alcohol and *cis*-selective reduction with triethylsilane as the key steps.

The synthesis of (+)-isolaurepan **1c** started from commercially available 1,6-hexanediol **2** as illustrated in Scheme 1. Thus, selective mono hydroxyl protection of **2** with *p*-methoxybenzyl bromide in the presence of NaH gave the monoprotected diol **3**

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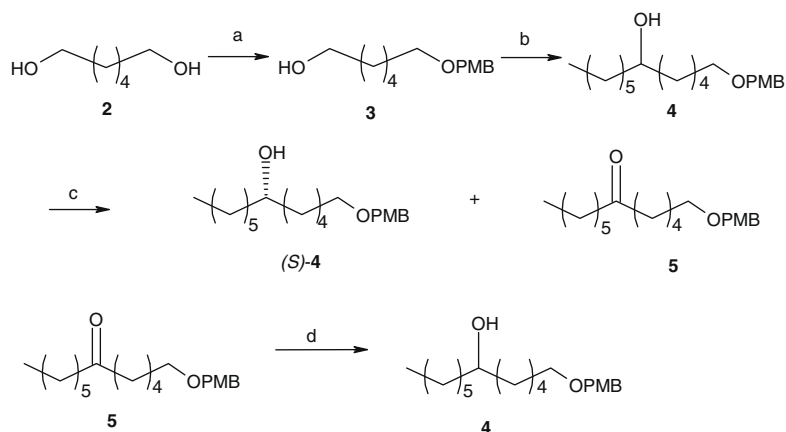
Scheme 1. Reagents and conditions: (a) *p*-CH₃OC₆H₄CH₂Br, NaH, dry DMF, cat. TBAI, 0 °C to rt, 1 h, 85%; (b) (i) (COCl)₂, DMSO, Et₃N, dry CH₂Cl₂, −78 °C, 2 h; (ii) *n*-C₆H₁₃MgBr, THF, 0 °C to rt, 1 h, 91%; (c) (*S,S*)-Salen–Mn^III(Cl) (0.02 equiv), KBr (0.8 equiv), PhI(OAc)₂ (0.7 equiv), H₂O/CH₂Cl₂ 2:1, rt, 30 min, 45% for (*S*)-**4** and 43% for **5**; (d) NaBH₄, MeOH, 4 h, 89%.
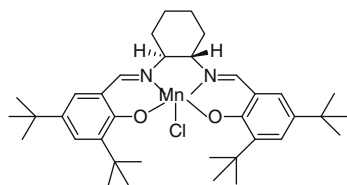

Figure 2. (*S,S*)-Salen–Mn^IIICl complex.

in 85% yield. This was then oxidized to the corresponding aldehyde under Swern conditions[9] and subsequently treated with the Grignard reagent derived from 1-bromohexane and Mg in THF at 0 °C to furnish the racemic alcohol **4** in 91% yield.

With substantial amounts of racemic alcohol **4** in hand, our next aim was to resolve this alcohol to obtain enantiomerically pure (*S*)-**4**. As illustrated in Scheme 1, the racemic alcohol **4** was subjected to oxidative resolution[10] using (*S,S*)-Salen–Mn^IIICl as catalyst (Fig. 2) to give the required optically active alcohol (*S*)-**4**[11] in 45% yield and 93% ee[12] along with the oxidized compound **5** in 43% yield which was easily isolated from the polar alcohol (*S*)-**4** using silica gel chromatography. Ketone **5** was recycled by conversion into the racemic alcohol **4** in 89% yield by reduction with NaBH₄ in MeOH.

As shown in Scheme 2, hydroxyl protection of (*S*)-**4** with *tert*-butyldimethylsilyl triflate in the presence of a catalytic amount of DMAP and 2,6-lutidine afforded the silyl ether **6** in 85% yield. Subsequent *p*-methoxybenzyl deprotection of the primary alcohol was carried out with DDQ in DCM/H₂O (18:1) to give the required alcohol **7** in 94% yield. Alcohol **7** was oxidized to the aldehyde with IBX followed by Grignard reaction with 1-bromopropane and Mg in THF at 0 °C to give the desired compound **8** in 62% yield. The newly formed secondary alcohol was oxidized using IBX to give ketone **9**[13] which on treatment with *p*-TSA in methanol afforded the required deprotected precursor **10**.

In order to generate the *cis*-disubstituted cyclic ether, ketone **10** was treated with Et₃SiH and TMSOTf which promoted reductive cyclization[6] to give exclusively the *cis* disubstituted cyclic 7-membered ether, isolaurepan **1c**,[14] in 84% yield. The configuration of the newly generated centres in **1c** can be deduced by ¹H-NMR and NOE experiments.[6] The physical and spectroscopic data of **1c** were identical with those reported.[6]

In conclusion, we have developed a short approach to *cis*- disubstituted oxepanes with high enantiomeric excess using (*S,S*)-Salen–Mn^III(Cl) as the catalyst. The *R* and *S* configurations of the *cis* ring can be manipulated simply by changing the catalyst in the resolution step. The synthetic strategy described here has significant potential for stereochemical variations and further extension to eight- and nine-membered rings and analogues. Currently, studies are in progress in this direction.
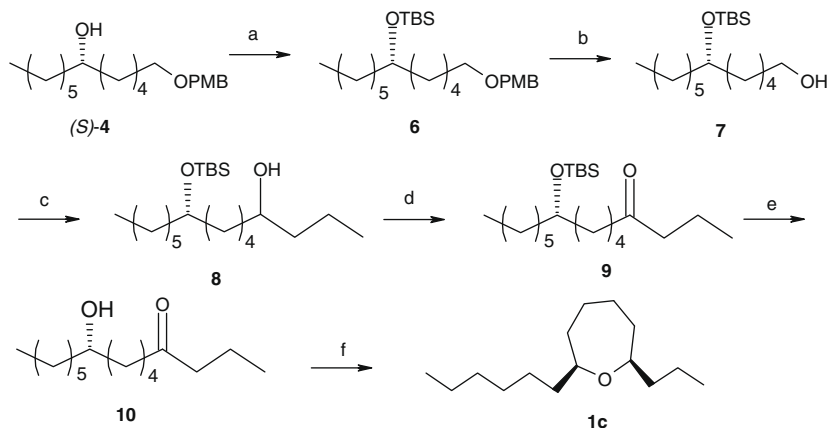
Scheme 2. Reagents and conditions: (a) TBS-OTf, 2,6-lutidine, cat. DMAP, dry CH₂Cl₂, 3 h, 0 °C, 85%; (b) DDQ, CH₂Cl₂/H₂O (18:1), rt, 1 h, 94%; (c) (i) IBX, EtOAc, 80 °C, 90%; (ii) *n*-C₃H₇MgBr, THF, 0 °C to rt, 1 h, 62%; (d) IBX, EtOAc, 80 °C; (e) *p*-TSA, MeOH, rt, 30 min; (f) Et₃SiH, TMSOTf, CH₂Cl₂, 0 °C, 1 h, 84%.

Acknowledgements

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11. The spectal data of (*S*)-**4**: Pale yellow oil. $[\alpha]_D^{25}$ +2.35 (*c* 1.7, CHCl$_3$); IR (CHCl$_3$): ν 3443, 2932, 2400, 1646, 1463, 1215, 1049, 759 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.89 (t, J = 6.7 Hz, 3H), 1.22–1.61 (m, 18H), 3.44 (t, J = 6.4 Hz, 2H), 3.57 (m, 1H) 3.80 (s, 3H), 4.43 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, CHCl$_3$): δ 14.0, 22.5, 25.4, 25.6, 26.2, 29.3, 29.6, 31.8, 37.4, 55.2, 55.2, 69.9, 71.8, 72.4, 113.6, 127.1, 129.2, 130.6, 158.9. Anal. Calcd for C$_{20}$H$_{34}$O$_3$ (322.48): C, 74.49; H, 10.63. Found: C, 74.26; H, 10.85.
12. The ee was measured by HPLC using a Chiralcel OD column (isopropyl alcohol/petroleum ether = 1:99); flow, 1.0 ml/min.
13. The spectral data of **9**: Colourless oil. $[\alpha]_D^{25}$ +6.0 (*c* 0.97, CHCl$_3$); IR (CHCl$_3$) ν = 2932, 2400, 1710, 1215, 1051, 759 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.92 (t, J = 7.4 Hz, 6H), 1.27–1.30 (m, 10H), 1.39–1.41 (m, 4H), 1.59–1.61 (m, 4H), 2.36–2.39 (m, 4H), 3.60, (m, 1H); ^{13}C NMR (50 MHz, CHCl$_3$): δ 0.5, 18.6, 18.9, 22.2, 23.0, 27.5, 28.9, 29.9, 30.1, 30.8, 34.4, 36.8, 41.7, 41.9, 47.7, 49.6, 81.6, 81.8, 82.1, 216.3; Anal. Calcd for C$_{21}$H$_{44}$O$_2$Si (356.66): C, 70.72; H, 12.43. Found: C, 70.58; H, 12.61.
14. The spectral data of **1c**: Colourless oil $[\alpha]_D^{25}$ +1.5 (*c* 0.97, CHCl$_3$); lit.[6] $[\alpha]_D^{24}$ +1.5 (*c* 0.97, CHCl$_3$); IR (CHCl$_3$) ν = 2950, 2920, 2850, 1465, 1455, 1375, 1340, 1140, 1100; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 1.26–1.44 (m, 10H), 1.47–1.55 (m, 8H), 1.65–1.73 (m, 4H), 3.37–3.39 (m, 2H); ^{13}C NMR (50 MHz, CHCl$_3$): δ 14.0, 19.4, 22.6, 25.3, 26.2, 29.3, 31.8, 36.8, 36.9, 37.4, 39.6, 80.0, 80.3.