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A Facile Synthesis of an Oxatricyclic *trans-syn-trans*-Substituted Oxepanyl Framework[1]

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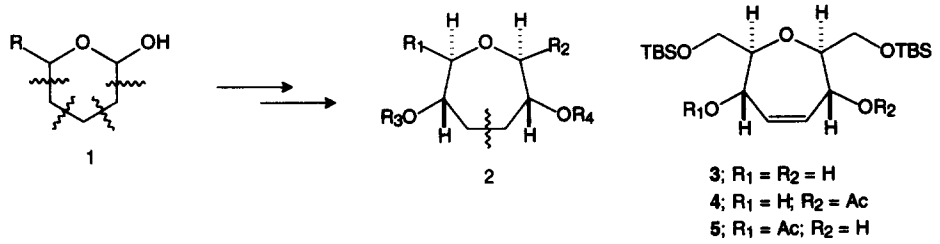
Abstract: The regio- and stereochemistry of iodine-promoted transannular ring expansion of cyclic *trans*-1,2-epoxy-5(E)-ene systems is used to synthesise *trans,syn,trans*-substituted oxepanyl subunits. © 1997 Elsevier Science Ltd.

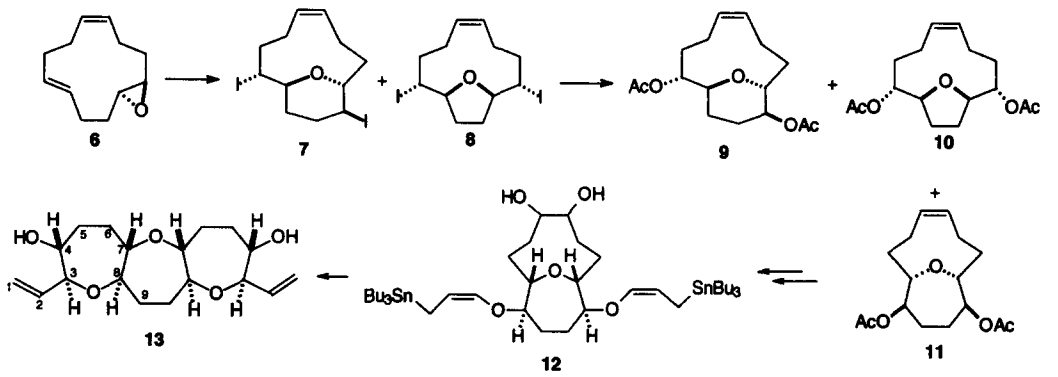
Oxepane rings often occur in marine polyether toxins as partial structures of brevetoxins, ciguatoxins and related compounds,[2] which have a *trans*-fused ring system to other six- to nine-membered with two *syn*-substituents neighbouring to the oxygen atom of cyclic ethers. New methods for the stereoselective synthesis towards a ring such as **2** using highly functionalized glycosides (**1**) *via* ring opening of the oxane followed by recyclization to oxepanyl derivatives are receiving much attention[3] (Scheme 1).



Scheme 1

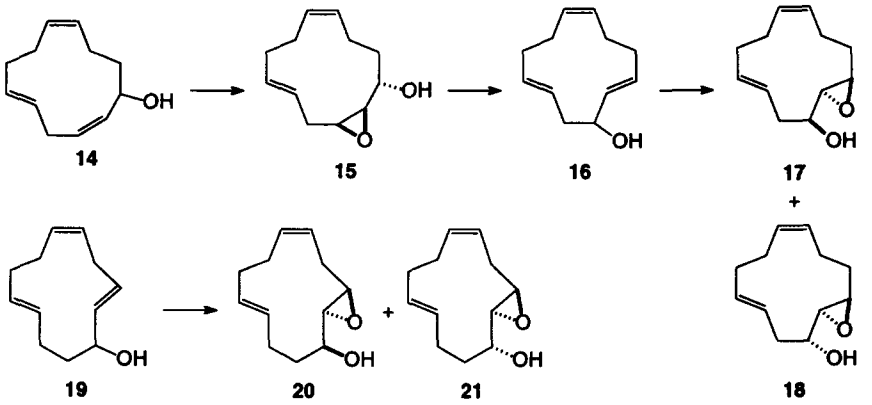
As an alternative to this work, we have developed a methodology, using non-carbohydrate precursors, based on electrophilic intramolecular oxirane ring expansion of cyclic *cis*-epoxy alkenes followed by C-C bond fragmentation of the resulting bridged oxabicyclic systems.[4] This method allows, for instance, the synthesis of the *meso*-C_8-*trans-syn-trans* oxepanyl subunit **3**.[5] The efficiency of the synthesis of the optically pure monoacetates **4** and **5**[4] makes this compound an interesting starting point for the synthesis of *trans*-fused polyether targets including ciguatoxin and related substances.[3d] As an extension of this methodology including

trans-epoxy derivatives, epoxide **6** was submitted to oxirane ring expansion by treatment with I_2/CH_2Cl_2/cat. $Ti(^iPrO_4)$ to give a 1:3 mixture of expanded diiodo oxacycles **7** and **8** in 95% yield (Scheme 2).



Scheme 2

Silver ion-induced solvolysis of the mixture **7** and **8** (AgOAc / $CHCl_3$:AcOH (4:1) / 40-45 °C / 24 h) gave a mixture of diacetates **9**, **10** and **11** in a 1.5 : 0.5 : 1 ratio (88% yield).[6] The structures of *meso* diacetates **10** and **11** were confirmed by X-ray crystallographic analysis.[7,8] Compound **11** possesses the required oxygenated pattern and was converted *via* the diallylstannane **12** to the *meso* oxatricyclic (7 : 7 : 7) system **13** (51% yield from **9**),[9] following a sequence of reactions similar to that previously reported by us for the synthesis of its (8 : 6 : 7) homologue.[4]

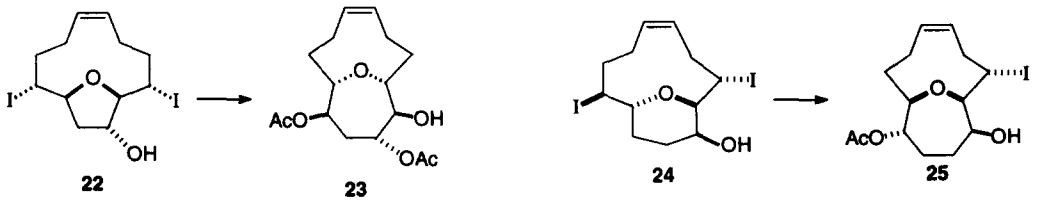


Scheme 3

For the construction of functionalized oxepanyl systems, the pairs of epoxy alkenols **17**, **18** and **20**, **21** were synthesized (Scheme 3). Isomerization of the readily available *cis*-alkenol **14**[4] to the *trans*-isomer **16** was achieved *via* epoxide **15** following the Wharton procedure[10] (67% overall yield). Allylic epoxidation of **16** with *t*-BuOOH / $Ti(^iPrO)_4$ / (±) DET / CH_2Cl_2 / -20 °C gave a 1:1 mixture of diastereomers **17** and **18**. The structures of both epoxy alcohols were proven by X-ray crystallographic analysis.[11,8] Conversion of epoxide **6**

to the *trans*-alkenol **19** can be clearly accomplished with LDA as base.[12] Allylic epoxidation of **19** under the above-mentioned conditions gave a 3:1 mixture of epoxyalkenols **20** and **21** whose structures were determined by X-ray analysis.[13,8]

The epoxides **17**, **18**, **20** and **21** appear to serve as promising templates for stereoselective electrophilic expansions of the oxirane ring leading to cyclododecane-containing target molecules with multiple functionality and the possibility to be further converted into *trans,syn*-substituted oxacyclic systems. Two examples are recorded in Scheme 4: Iodine-induced ring expansion of the epoxy-alcohols **18** (*erythro*) and **20** (*threo*) led to smooth conversion to diiodides **22** and **24** (93% and 96% yields, respectively). Treatment of **22** with AgOAc in refluxing dioxane-AcOH (20:1) gave a complex mixture of deiodinated compounds (68% yield) from which diacetate **23**[14] was isolated as the major component (18% yield). The reaction was complicated by partial migration of the acyl groups. Silver (I)-assisted solvolysis of the diiodoalcohol **24** with AgOAc in AcOH:$CHCl_3$ (2:1) underwent instant reaction to give **25**[15] in 89% yield.



Scheme 4

Work is underway in our laboratories to convert the new epoxyalkenols described here to a variety of *ortho*-condensed oxepanyl systems. The mild conditions and high yields associated with the general reaction conditions make this an attractive method for the construction of *trans*-fused polyethers.

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References and notes

1. Dedicated to Professor Waldemar Adam on the occasion of his 60th birthday on July 16, 1997.
2. Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897-1909.
3. (a) Ravelo, J.L.; Regueiro, A.; Rodríguez, E.; Vera, J.; Martín, J.D. *Tetrahedron Lett.* **1996**, *37*, 2869-2872. (b) Sasaki, M.; Inoue, M.; Tachibana, K. *J. Org. Chem.* **1994**, *59*, 715-717. (c) Tanaka, S.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7801-7804. (d) For a review, see: Alvarez, E.; Candenas, M.L.; Pérez, R.; Ravelo, J.L.; Martín, J.D. *Chem. Rev.* **1995**, *95*, 1953-1980.
4. Alvarez, E.; Díaz, M.T.; Ravelo, J.L.; Regueiro, A.; Vera, J.A.; Zurita, D.; Martín, J.D. *J. Org. Chem.* **1994**, *59*, 2848-2876.
5. Alvarez, E.; Díaz, M.T.; Pérez, R.; Martín, J.D. *Tetrahedron Lett.* **1991**, *32*, 2241-2244.
6. All new compounds reported herein have been fully characterized by IR, high-field 1H and 13C NMR, high-resolution mass spectrometry and combustion analysis. The stereochemical assignments are reliably based on extensive NOE studies.
7. Crystal data for *compound 11* (diol): $C_{12}H_{20}O_3$, monoclinic, a = 5.185 (9), b = 16.145 (18), c = 13.492 (29) Å, β = 92.650 (16)°, V = 1128.7 (3) $Å^3$, space group $P2_1/n$ (# 14), Z = 4. The final discrepancy

index was R = 0.051 for 420 observed reflections [I ≥ 3σ(I), 3° ≤ 2θ ≤ 116°]. *Compound 10*: $C_{16}H_{24}O_5$, monoclinic, a = 8.361 (15), b = 23.160 (35), c = 9.306 (13) Å, β = 114.502 (13)°, V = 1639.6 (5) Å^3, space group $P2_1/n$ (# 14), Z = 4. The final discrepancy index was R = 0.095 for 1260 observed reflections [I ≥ 3σ(I), 3° ≤ 2θ ≤ 116°].

8. Details of the crystal structures determination may be obtained from the Director of the Cambridge Crystallographic Data Center, University of Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW (UK) on quoting the full journal citation.
9. Data for **13** (diacetate): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddd, J = 17.2, 10.6, 5.2 Hz, H-2), 5.30 (1H, ddd, J = 17.2, 1.7, 1.7 Hz, H-1), 5.11 (1H, ddd, J = 10.6, 1.7, 1.7 Hz, H-1), 4.92 (1H, br s, H-4), 4.05 (1H, dddd, J = 6.8, 5.2, 1.7, 1.7 Hz, H-3), 3.49 (1H, ddd, J = 9.1, 6.5, 4.5 Hz, H-8), 3.36 (1H, ddd, J = 9.1, 9.1, 5.0 Hz, H-7), 2.05 (2H, m, 2xH-9), 1.86 (2H, m, H-5, H-6), 1.59 (2H, m, H-5, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, (s, C=O), 136.5 (d, C-2), 115.8 (t, C-1), 85.3 (d, C-7), 82.3 (d, C-3), 82.3 (d, C-8), 76.4 (d, C-4), 29.6 (t, C-9), 28.3 (t, C-5), 23.4 (t, C-6), 21.3 (q, $\underline{C}H_3CO_2$).
10. Wharton, P.S. *J. Org. Chem.* **1961**, *26*, 4781-4782.
11. *Compound 17*, $C_{12}H_{18}O_2$, monoclinic, a = 8.229 (10), b = 5.155 (6), c = 13.389 (20) Å, β = 98.680 (16)°, V = 561.5 (3) Å^3, space group $P2_1$, Z = 2. The final discrepance index was R = 0.041 for 531 observed reflections [I ≥ 3σ, 3° ≤ 2θ ≤ 110°]. *Compound 18*, $C_{12}H_{18}O_2$, monoclinic, a = 13.224 (34), b = 5.866 (15), c = 15.431 (20) Å, β = 106.2 (19)°, V = 1149.5 (5) Å^3, space group $P2_1/C$, Z = 4. The final discrepance index was R = 0.071 for 467 observed reflections [I ≥ 1.5σ, 3° ≤ 2θ ≤ 110°].
12. Gorzynski-Smith, J. *Synthesis* **1984**, 629-656.
13. *Compound 20* (*p*-bromobenzoate) $C_{19}H_{21}BrO_3$, monoclinic, a = 28.860 (2), b = 16.655 (12), c = 7.380 (2) Å, β = 100.29 (4)°, V = 3491 (4) Å^3, space group C2/c, Z = 8. The final discrepance index was R = 0.059 for 3364 observed reflections [I > 2σ(I)]. *Compound 21* (*p*-bromobenzoate) $C_{19}H_{21}BrO_3$, monoclinic, a = 14.650 (10), b = 7.291 (10), c = 16.658 (10) Å, β = 102.133 (10)°, V = 1740 (3) Å^3, space group $P2_1/n$, Z = 4. The final discrepance index was R = 0.036 for 3998 observed reflections [I > 2σ(I)].
14. Data for diacetate **23**: Crystalline solid, mp 91.0 - 91.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 5.60 (m, 2H), 4.95 (dd, J = 9.2, 9.2 Hz, 1H), 4.88 (ddd, J = 8.0, 4.0, 4.0 Hz, 1H), 3.45 (dd, J = 9.2, 8.9 Hz, 1H), 3.17 (m, 1H), 3.13 (m, 1H), 2.76 (m, 2H), 2.16 (m, 2H), 2.07 (s, 6H), 1.99 (m, 4H), 1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 170.7, 170.6, 130.4, 129.9, 84.9, 83.5, 76.7, 74.9, 74.8, 34.3, 32.5, 30.8, 22.2, 21.8, 21.2, 21.2; IR (KBr): 3454, 3066, 2917, 2855, 1736, 1436, 1382, 1249, 1136, 1050, 1033, 971, 728 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.66; H, 7.56.
15. Data for monoacetate **25**: Crystalline solid, mp 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 5.72 (m, 2H), 4.82 (ddd, J = 8.0, 4.3, 4.3 Hz, 1H), 4.66 (ddd, J = 10.7, 5.0, 2.0 Hz, 1H), 4.37 (m, 1H), 3.48 (dd, J = 10.7, 1.7 Hz, 1H), 3.38 (ddd, J = 14.8, 9.8, 5.0 Hz, 1H), 3.20 (ddd, J = 12.4, 8.0, 4.6 Hz, 1H), 2.66 (dddd, J = 15.8, 11.8, 11.8, 7.2 Hz, 1H), 2.33 (ddd, J = 16.0, 4.0, 1.6 Hz, 1H), 2.11 (m, 1H), 1.91 (s, 3H), 1.87 (m, 2H), 1.82 (m, 1H), 1.75 (m, 1H), 1.70 (m, 1H), 1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 170.2, 132.1, 127.4, 92.1, 85.1, 77.8, 67.8, 33.3, 31.9, 30.5, 29.3, 24.8, 23.0, 21.4; IR ($CHCl_3$): 3619, 3448, 2975, 2400, 1730, 1522, 1424, 1218, 1023 cm^{-1}; Anal. Calcd for $C_{14}H_{21}IO_4$: C, 44.22; H, 5.53. Found: C, 44.32; H, 5.55.

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