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Epoxide-Initiated Cationic Polyene Cyclisations

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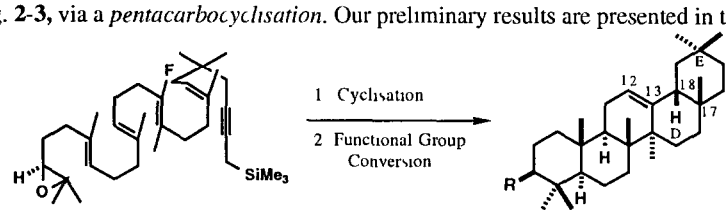
Abstract: The Lewis acid (2-propoxy)titanium trichloride is an efficient reagent for epoxide-initiated polyene cyclisations. Thus, **4** underwent tricyclisation to yield tricyclic products **5-7** in 73 % yield. The tetraene epoxide **1** gave pentacycle **15** in 21 % yield The latter is the first example of a cationic *pentacarbocyclisation*

The first example of an epoxide-initiated polyene cyclisation was reported[1] before its biological significance was discovered, after which the field became very active[2] to an extent that this type of cyclisation has been accepted as a standard method for the formation of fused carbocyclic rings.[3] The attraction of this synthetic construction is the high degree of molecular complexity furnished in a single step. Biomimetic cyclisations that involve the formation of two rings can be achieved in respectable yield,[3a-k] but the application of this reaction in the construction of three rings has resulted in low yields of fully cyclised products (5-20 %).[3l-q] The only example of an epoxide-initiated tetracyclisation furnished (±)-allopregnanolone in ~2 % yield.[3r] The problems with such cyclisations can be attributed to two factors: 1. non-cyclisation reactions of the epoxide, and 2. non-stereoselective cyclisation of the polyene. The former may be alleviated to a considerable extent by judicious choice of the acid used to promote the cyclisation, and the latter by appropriate design of the epoxide polyene. Under ideal circumstances it should be feasible to synthesise polycyclic triterpenoids in a single step from an acyclic substrate. Thus it was our aim to design a suitably functionalised polyene epoxide substrate, e.g. **1**, which, upon carefully controlled acid-promoted reaction, would give direct access to the oleanane series of triterpenes, e.g. **2-3,** via a *pentacarbocyclisation*. Our preliminary results are presented in this Letter.



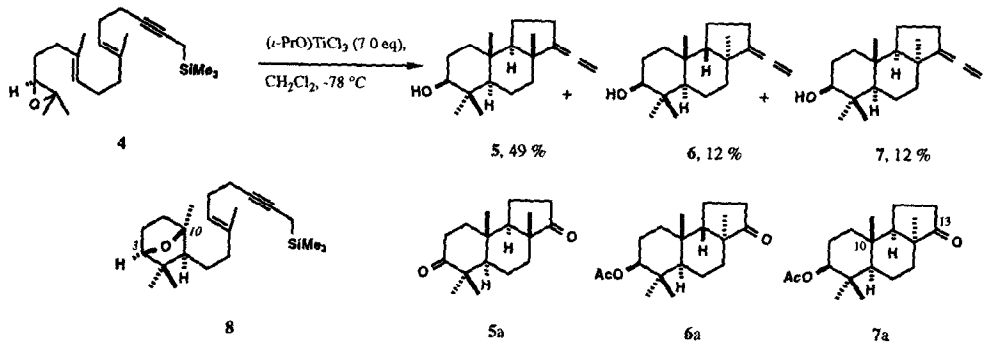
1

2, β-Amyrin (R = OH)
3, Olean-12-ene (R = H)

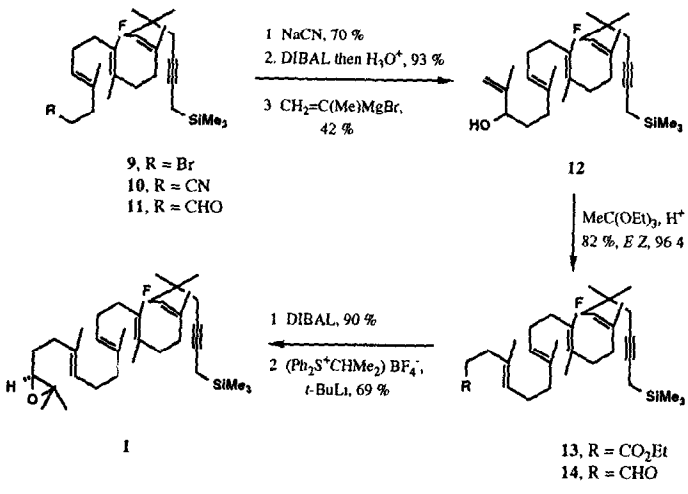
Epoxide **1** incorporates several key features which have been shown in a related series to promote and control the cyclisation. The fluorine atom cation-stabilising (C-S) auxiliary[4] at *pro*-C13 would be expected not only to enhance the cyclisation but also to control the regiochemistry to give the six-membered C-ring.[4c] The olefinic bond of **1**, *pro*-C17-18, involved in the formation of ring D has the (*Z*)-stereochemistry so that, according to the Stork-Eschenmoser principle, the closure would give the required D/E *syn-cis* configuration in **2** and **3**. The cyclisation would be terminated by the highly nucleophilic propargyl silane group.[4c-d]

Model studies with the epoxy dienyne **4** gave very encouraging results.[5] Treatment of **4** with (2-propoxy)titanium trichloride[6] (7.0 eq, CH_2Cl_2, -78 °C, 10 min) resulted in facile cyclisation to yield three tricyclic products in a combined yield of 73 % (**Scheme 1**) [7,8] The major product of the cyclisation proved to be **5** (49 %) and the minor products were identified as the two stereoisomers **6** (12 %) and **7** (12 %). The

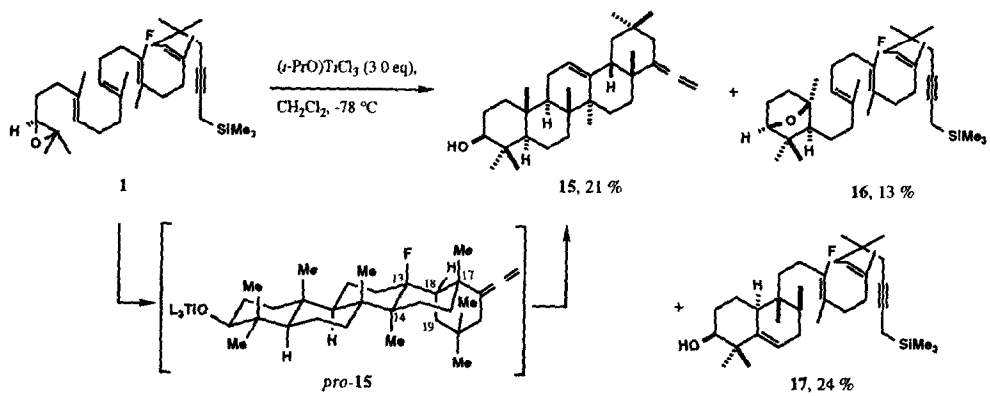
Scheme 1:



Scheme 2:



Scheme 3:



cyclisation mixture was initially acetylated and then purified by column chromatography on silver nitrate impregnated silica gel which separated **5** as the corresponding acetate. Tricycle **5** was the result of a *trans-anti-trans* closure of **4** via a chair-chair transition state, which corresponds to the synthetically prefered reaction pathway. The structure of **5** was proposed by interpretation of NMR data and then confirmed by transformation [(a), Ac_2O, DMAP; (b), O_3; (c), NaOMe; (d), PCC] to the diketone **5a** which is a degradation product of malabaricol.[9] The two minor tricyclic products **6** and **7** were converted [(a)+(b)] to the corresponding acetoxy ketones, **6a** and **7a** respectively, which were separable by chromatography. Tricycle **6**, the B-ring boat isomer, was identified by single crystal X-ray analysis of ketone **6a**,[10] and the stereochemistry of **7** was tentatively assigned on the basis of NMR data of **7a**.[11] Attempted cyclisation of **4** with $TiCl_4$ resulted in decomposition and the use of $(i\text{-PrO})_{1.5}TiCl_{2.5}$ gave rise to the formation of bicyclic ether **8** (15 %) at the expense of **5-7**.[12] Hence the constitution of the titanium catalyst is a key feature of the cyclisation. Cyclisation of **4** in nitromethane gave an increased selectivity for **5**, (**5**:**6**:**7**, 8:1:1), but with lower overall yield.

The cyclisation substrate, **1**, was synthesised from the known bromo triene **9**[4d] according to the procedure outlined in **Scheme 2**.[7] Thus, treatment of **9** with NaCN gave nitrile **10** which was then reduced with DIBAL to aldehyde **11**. Reaction of **11** with CH_2=C(Me)MgBr gave alcohol **12** which underwent ortho ester Claisen rearrangement[13] to ester **13** with high stereoselectivity (96:4). The synthesis was completed by reduction of **13** with DIBAL, and alkylation of the resulting aldehyde **14**, with the sulphur ylide derived from diphenyl-(2-propyl)sulphonium tetrafluoroborate,[14] gave the (*E,E,Z,Z*)-epoxide **1**.[15]

The cyclisation of epoxide **1** was initially investigated on a semi-preparative scale to determine the optimum conditions for the formation of the pentacyclic products. The propensity of several Lewis acids to promote cyclisation was investigated under standardised conditions. As with substrate **4**, the most successful conditions for the cyclisation of **1** employed (2-propoxy)titanium trichloride, giving rise to three major products, **15-17**, for a combined GC yield of 58-72 % of the crude reaction mixture, and these were separable by column chromatography. Thus, treatment of epoxide **1** on a preparative scale with $(i\text{-PrO})TiCl_3$ (3.0 eq) in CH_2Cl_2 at -78 °C for 10 min gave pentacycle **15** in 21 % GC yield (10 % isolated yield after recryst. to >98 % purity; mp 184-186 °C) (**Scheme 3**).[7, 16] The stereochemistry of **15** was established from spectral data and by correlation with the data for the ABCD- and BCDE-rings of several closely related natural, and non-natural, oleanenes including β-amyrin (**2**).[4c-d, 17] The fluoropentacycle *pro*-**15** was not isolated but evidently underwent *in situ* regioselective dehydrofluorination (C12-13), to **15**, in order to relieve the transannular (C13-F v C17-Me, C19 v C14-Me) and Pitzer (C13-F v C18-H v C17-Me) strain associated with D/E *syn-cis* configuration.[18] The other major products of the cyclisation were the bicyclic ether **16** (13 %)[12, 19] and a rearranged bicyclic carbocycle (24 %), tentatively assigned as **17**,[20] both resulting from only partial cyclisation of the polyene.

In conclusion, we have performed the first example of a high yielding epoxide-initiated tricarbocyclisation and the first example of an epoxide-initiated pentacarbocyclisation, **1**→ **15**. The latter proceeds with very respectable yield when considering the degree of molecular complexity furnished in a single step, and when compared to previous cyclisation studies. These two examples demonstrate that (2-propoxy)titanium trichloride is an effective reagent for promoting this type of reaction.

Acknowledgements:
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6 A solution of (2-propoxy)titanium trichloride (ca 0 5 M in dichloromethane) was prepared by the dropwise addition of titanium(IV) chloride (3 0 mL, 1 0 M in dichloromethane, 3 0 mmol) to a stirred solution of titanium(IV) isopropoxide (0 30 mL, 1.0 mmol) in dichloromethane (4 7 mL) under Ar at 23 °C

7 Satisfactory spectroscopic data, together with microanalytical and/or HRMS data, were obtained for all new compounds

8 Yields were determined by GC analysis of the reaction product mixture using tetracosane as an internal standard.

9 (a), Chawla, A ; Dev, S *Tetrahedron Lett* **1967**, 4837-4843, (b), Paton, W F; Paul, I C *Tetrahedron Lett* **1979**, 4153-4154

10 This structure determination was performed by F S Tham and R K Kullnig, Rensselaer Polytechnic Institute, Troy NY

11 The axial C10-Me resonance at δ_H 1 17 ppm of **7a** is consistent with deshielding by the C13 ketone The alternative *syn-cis* B/C product would have no similar downfield shift

12 The trapping of the carbenium ion at *pro*-C10 by transannular attack of the *pro*-C3 metal alkoxide is commonly observed in epoxide-initiated cyclisations of this nature See: ref 1, 3a-c, 3n, 3r

13 Johnson, W S.; Werthemann, L ; Bartlett, W R , Brocksom, T J ; Li, T -t ; Faulkner, D J ; Petersen, M R *J Am Chem. Soc.* **1970**, *92*, 741-743

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15 For **1** Oil, Bp 117 °C (oven temp) at 0 005 mmHg, R_f 0 37 (9 1 hex-ether); IR (film) ν 2920, 2890, 2840, 2210, 1690, 1655, 1435, 1365, 1235, 840, 690 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 5 17 (t, *J* = 6 5 Hz, 1 H), 5 17-5 11 (m, 2 H), 2 70 (t, *J* = 6 3 Hz, 1 H), 2 28-1 95 (m, 14 H), 2 02 (t, *J* = 2 7 Hz, 2 H), 1 97 (d, *J* = 7 8 Hz, 2 H), 1 72 (d, *J* = 1.1 Hz, 3 H), 1.71-1 58 (m, 2 H), 1 61 (s, 3 H), 1 61 (s, 3 H), 1 58 (d, *J* = 2 5 Hz, 3 H), 1 44 (t, *J* = 2 6 Hz, 2 H), 1 30 (s, 3 H), 1.26 (s, 3 H), 0.92 (s, 6 H), 0 09 (s, 9 H); HRMS calcd for $C_{35}H_{59}FOSi$, 542 4319 Found, 542 4330, Anal calcd for $C_{35}H_{59}FOSi$: C, 77 43; H, 10 95 Found C, 77 59; H, 10 84

16 For **15**: Clusters of colourless micro-needles from acetonitrile; Mp 184-186 °C; R_f 0.15 (4.1 hex-ether); IR ($CHCl_3$) ν 2920, 2900, 2840, 1940, 1445, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5 21 (t, *J* = 3 6 Hz, 1 H), 4 62 (dd, *J* = 9 0, 3 9 Hz, 1 H), 4 54 (dd, *J* = 9 2, 4 3 Hz, 1 H), 3 26-3 18 (m, 1 H), 2 16-2 01 (m, 3 H), 1 92-1 73 (m, 5 H), 1 66-0 70 (m, 14 H), 1.16 (s, 3 H), 1 00 (s, 3 H), 0.99 (s, 3 H), 0 97 (s, 3 H), 0.94 (s, 3 H), 0 92 (s, 3 H), 0 86 (s, 3 H), 0 79 (s, 3 H), LRMS m/z (relative intensity) 450 (4 %, M^+, $C_{32}H_{50}O$), 435 (6), 281 (3), 242 (20), 227 (100), 213 (15), 207 (11), 187 (13), 173 (13), 133 (11), 119, (12), 69 (18), HRMS calcd for $C_{32}H_{50}O$, 450 3862 Found, 450 3848; Anal calcd for $C_{32}H_{50}O$ C, 85 27, H, 11 18 Found C, 85 12, H, 11 01 **TBDMS ether** of **15** ^1H NMR (400 MHz, $CDCl_3$) δ 5 21 (t, *J* = 3 5 Hz, 1 H), 4 62 (dd, *J* = 9 1, 3 9 Hz, 1 H), 4 54 (dd, *J* = 9 1, 4 2 Hz, 1 H), 3 18 (dd, *J* = 11 0, 4 5 Hz, 1 H), 2 16-2 01 (m, 3 H), 1 92-1 72 (m, 5 H), 1 64-0 68 (m, 13 H), 1 15 (s, 3 H), 0 99 (s, 3 H), 0 97 (s, 3 H), 0 93 (s, 3 H), 0 93 (s, 3 H), 0 91 (s, 3 H), 0 89 (s, 9 H), 0 86 (s, 3 H), 0 75 (s, 3 H), 0 03 (s, 6 H)

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18 Cf the analogous Lewis acid-promoted regiospecific dehydrofluorination observed in the synthesis of β-amyrin, see ref 4d

19 For **16**: Partial ^1H NMR (400 MHz, $CDCl_3$) δ 3 71 (d, *J* = 5 2 Hz, 1 H), 1 32 (s, 3 H), 1 04 (s, 3 H), 1 01 (s, 3 H).

20 Spectroscopic data indicates only partial cyclisation because **17** exhibits characteristic signals arising from the dienyl terminus of the polyene substrate The constitution of the AB-rings was determined by interpretation of spectroscopic data and comparison with a similarly rearranged triterpene, see ref 3e For **17**· Partial ^1H NMR (400 MHz, $CDCl_3$) δ 5 46 (t, *J* = 3 2 Hz, 1 H), 3 44 (d, *J* = 8 2 Hz, 1 H), 1 10 (s, 6 H), 0 87 (s, 3 H), 0 82 (d, *J* = 6 7 Hz, 3 H)

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