Highly Diastereoselective Synthesis of Manoyl Oxide Derivatives by $TiCl_4$-Catalyzed Nucleophilic Cleavage of Ambracetal Derivatives

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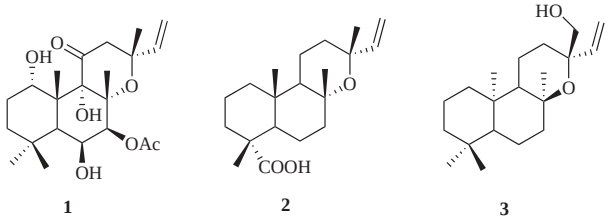
Abstract: The treatment of acetal **11** with KCN and $AlCNEt_2$ in the presence of $TiCl_4$ produces in high diastereoselectivity 2-cyanooxane **14**, which can be easily converted into manoyl oxide derivatives. Using this strategy, 19-hydroxymanoyl oxide **20**, diterpene from *P. viscosum*, was prepared from communic acids **7a**–**c** after an 8-steps sequence in a 17% overall yield.

Key words: natural products, acetal cleavage, manoyl oxides, Lewis acids, labdane diterpenes

Manoyl oxides are a type of diterpene, which present wide-reaching, interesting biological activities. A representative example of such a diterpene is forskolin (**1**), the synthesis of which has been the subject of many studies[1] because of its potent activity.[2]

Recent studies have revealed that less functionalized manoyl oxides, as well as their derivatives, exhibit a considerable degree of biological activity: antimicrobial,[3] antibacterial,[4] adenylate-cyclase modifier,[5] antitumor,[6] cytotoxic,[7] antilehmaniosis[8] and antileucemic, causing cell apoptosis.[9] Compound **2** is a potent immunosuppressive[10] and ent-manoyl oxide **3** presents anti-inflammatory activity (Figure 1).[11]



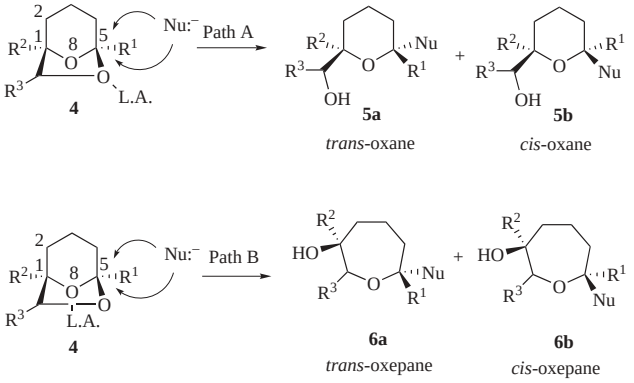
1 **2** **3**

Figure 1

During the last few years, some such compounds have been prepared by chemical or microbiological procedures[3,5,7–9,12] in order to study structure-activity relationships and to prepare compounds that are more active than those of natural origin.

Following our research into the synthesis of bioactive compounds starting from enantiomerically pure synthons obtained from natural sources, we have investigated the nucleophilic cleavage of bicyclic acetal **11** as a method to gain manoyl oxide derivatives. Acetal **11** is a suitable intermediate to elaborate terpenoids having ring A functionalization.[13]

Lewis acid-catalyzed cleavage of the 6,8-dioxabicyclo[3.2.1]octane derivatives **4** leads to oxane **5** and oxepane type compounds **6** in variable proportions, depending upon the bicyclic acetal **4** framework and the nucleophile structure (Scheme 1).



Scheme 1

Significant amounts of oxepane derivatives, frequently the main product, result when cyanide (TMSCN) is used as the nucleophile.[14] Oxanes are preferred when other nucleophiles, such as DIBAH, Et_3SiH, Ph_3SiH or allyltrimethylsilane, are used.[15] The selective formation of oxepanes by reductive and allylative cleavage of bicyclic acetals, such as **4**, using chelation of $TiCl_4$, has recently been described; thus, oxepane **6** is the only product when R^2 is an alkoxymethyl group, the chelation of which favours the coordination of the Lewis acid with O-8 (path B in Scheme 1).

Concerning the C-5 stereochemistry, stereoselective reductive cleavages, which enable the obtention of *trans*- or *cis*-oxanes, by selecting the nucleophile and the reaction

Table 1 Oxidation of **9**, **10** with $OsO_4/NaIO_4$

Entry	Temperature	Reaction time	**11**:**12**:**13**	$OsO_4/NaIO_4$ (equiv)	Yield
1	r.t.	8 d	1:43:10	0.1:2.0	85%
2	60 ºC	14 h	1:20:10	0.1:2.0	89%
3	reflux	16 h	45:0:10	0.2:2.5	95%

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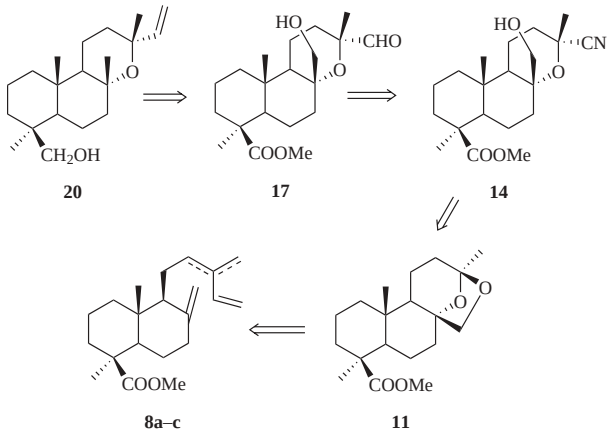
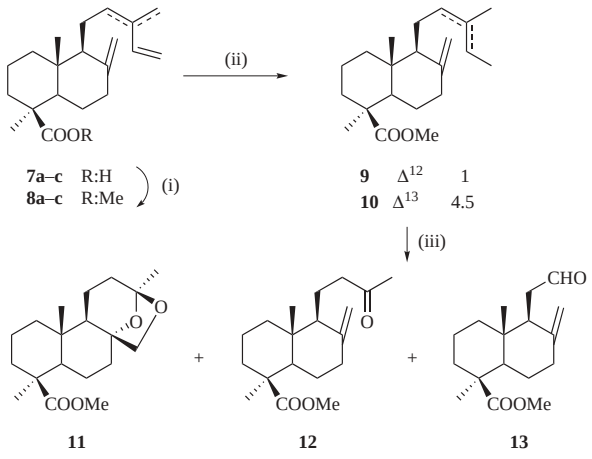


Scheme 2

temperature, have been reported; nevertheless, *trans*-oxanes are the main products during cyanoaddition processes.[14]

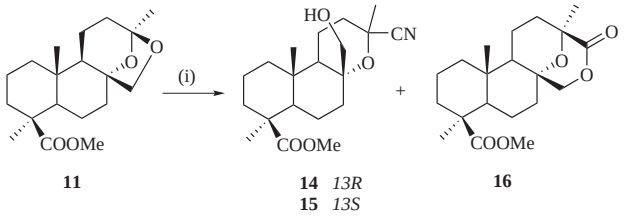
A possible route to manoyl oxide derivatives, such as **20**, based on the above results, is depicted in Scheme 2. Nitrile **14**, which results from the stereoselective Lewis acid-catalysed nucleophilic cleavage of the bicyclic acetal **11** with KCN, is a key intermediate. The methyl group on C-8 of **20** is elaborated after reduction of the corresponding sulphonic ester on C-17; whereas the C-13 vinyl group is obtained by Wittig reaction of the aldehyde **17**, which results from the reduction of **14**.



Scheme 3 (i) CH_2N_2, Et_2O, r.t., 5 min (100%). (ii) Na, *t*-BuOH, 80 ºC, 12 h (90%). (iii) OsO_4: 0.2%, $NaIO_4$, *t*-BuOH–H_2O (7:3).

The synthesis of **11** from communic acids **7a**–**c**, which has been previously reported by our group,[16] is considerably improved. Acetal **11** is directly obtained from the diene mixture **9** and **10**, resulting from the reduction of methyl esters **8a**–**c** with Na in *t*-BuOH, by refluxing with OsO_4/$NaIO_4$ in *t*-BuOH–H_2O. In this way, the synthesis is shortened by one step and the yield increased by more than 10% (Scheme 3, Table 1).

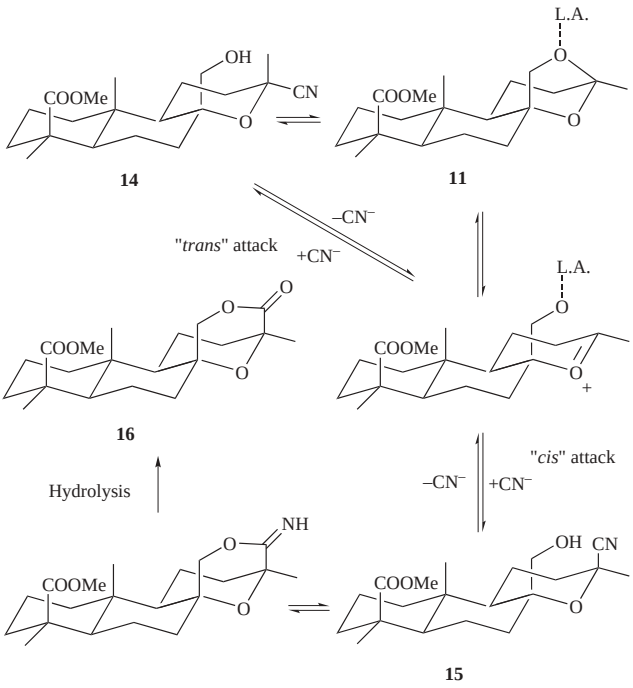
Subsequently, the behaviour of acetal **11** towards cyanide, in the presence of $TiCl_4$, was studied, and the most representative results of this are shown in Scheme 4 and Table 2. Treatment of **11** with $TiCl_4$, $AlEt_2CN$ and KCN, in the presence of 18-crown-6 ether affords variable amounts of epimeric 13-cyanooxanes **14** and **15**, or the lactone **16**, depending upon the reaction conditions. Oxane **14** is the main product at low temperatures. Lactone **16** is the only product under reflux; equimolar quantities of **14** and **15** result at room temperature. At no time were oxepane derivatives observed.



Scheme 4 (i) $TiCl_4$, $AlEt_2CN$, KCN, 18-crown-6-ether.

Table 2 Nucleophilic Cleavage of **11**[19,20,]

Entry	Temp.	Reacion time	**14**:**15**:**16**	Yield
1	–78 ºC	1 h	6:1:0	90%
2	r.t.	14 h	1:1:0	90%
3	reflux	22 h	0:0:1	70%

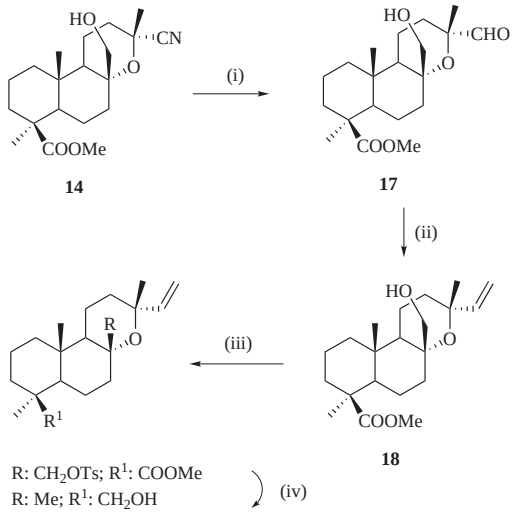


Scheme 5

The observed acetal ring opening regioselectivity could be attributed to the C_{17}–O–C_{13} oxygen accessibility and the high stability of the resulting tricyclic system. Furthermore, the above results reveal that **14**, which results from the nucleophilic attack by the less hindered α side of the oxocarbenium ion, is the kinetic product.

The lactone **16**, the isolation of which in related processes has not been reported,[14,17] is formed under thermodynamic conditions. Lactone **16** is irreversibly formed from **15**, which is equilibrated with its epimer **14** (Scheme 5). In support of this supposition is the fact that the treatment of **14** with KCN/ $AlEt_2CN$ and $TiCl_4$ at room temperature affords in high yield a 1:1 mixture of acetal **11** and lactone **16**.

The manoyl oxide framework of **14** was elaborated in accordance with the retrosynthetic Scheme 2. Treatment of **14** with DIBAH in THF at room temperature gives in high yield aldehyde **17**, which is converted into the vinyl derivative **18** after reaction with the methylenphosphorane. Reduction of tosyl derivative **19** by refluxing with $LiAlH_4$ in THF affords 19-hydroxymanoyl oxide **20**, diterpene isolated from *P. viscosum*.[18] Spectroscopic properties of **20** are identical to those of the natural compound (Scheme 6).



Scheme 6 (i) DIBALH, THF, 0 ºC–r.t., 1 h (80%). (ii) $MePPh_3Br$, *n*-BuLi, THF, 0 ºC, 45 min (80–90%). (iii) TsCl, Pyridine, r.t., 24 h (95%). (iv) $LiAlH_4$, THF, reflux, 48 h (50%).

In summary, the highly diastereoselective Lewis acid catalyzed cyanoaddition of **11** enables the synthesis of manoyl oxide derivatives from communic acids **7a**–**c**.

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(19) Typical Procedure for the Nucleophilic Cleavage of **11**; Synthesis of Oxanes **14** and **15**: To a stirred solution of **11** (0.25 g, 0.78 mmol), 18-crown-6-ether (0.57 g, 2.14 mmol) and KCN (0.2 g, 3.10 mmol) in CH_2Cl_2 (15 mL), was added $AlCNEt_2$ (1.0 M in CH_2Cl_2, 6.2 mL) and $TiCl_4$ (1.0 M in CH_2Cl_2,1.9 mL) at –78 ºC, under Ar atmosphere. The reaction mixture was then stirred at the indicated temperature during the time showed in Table 2. Then an aq 1 M $NaHCO_3$ solution (8 mL) was added and the resulting mixture was stirred for 3 h, and extracted with *t*-BuOMe (2 × 30 mL). The organic phase was successively washed with 5% aq $NaHCO_3$ (2 × 30 mL), water (2 × 30 mL), brine (2 × 30 mL), dried over anhyd Na_2SO_4 and evaporated to give a crude product which was chromatographed (hexane–*t*-BuOMe, 3:2) to yield **14** and **15**.
(20) All new compounds were fully characterized spectroscopically and had satisfactory HRMS data. Selected data:
Compound 14: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.58 (s, 3 H, Me-10a), 1.04 (dc, *J* = 13.7, 4.2 Hz, 2 H), 1.16 (s, 3 H, Me-7), 1.20–1.54 (m, 2 H), 1.57 (s, 3 H, Me-3), 1.65–2.30 (m, 11 H), 3.40 (dd, *J* = 11.1, 1.5 Hz, 1 H, 4a-CH_2OH-A), 3.60 (s, 3 H, 7-COOMe), 3.61 (d, *J* = 11.6 Hz, 1 H, 4a-CH_2OH-B).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4 (7-$COOCH_3$), 122.4 (3-CN), 79.3 (C-4a), 66.8 (C-3), 63.7 (4a-CH_2OH), 56.3* (C-10b), 51.3 (7-COOMe), 48.3* (C-6a), 43.7 (C-7), 38.8 (C-10), 37.9 (C-10a), 37.7 (C-8), 36.6 (C-6), 31.9 (C-2), 29.2 (Me-3), 28.5 (Me-7), 21.2 (C-5), 18.9 (C-9), 14.4 (C-1), 12.7 (Me-10a).
Compound 18: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.57 (s, 3 H, Me-20), 0.88 (dt, *J* = 13.3, 4.1 Hz, 1 H), 0.98 (dt, *J* = 12.9, 3.9 Hz, 1 H), 1.00–1.25 (m, 1 H), 1.17 (s, 3 H, Me-18), 1.28 (s, 3 H, Me-16), 1.65–1.95 (m, 7 H), 2.16 (d, *J* = 13.1 Hz, 1 H), 2.23 (dt, *J* = 12.7, 3.4 Hz, 1 H), 3.56 (dd, *J* = 10.5, 1.7 Hz, 1 H, 17-CH_2OH-A), 3.62 (d, *J* = 10.5 Hz, 1 H, 17-CH_2OH-B), 3.62 (s, 3 H, 19-COOMe), 4.99 (dd, *J* = 10.8, 1.1 Hz, 1 H, =CH_2), 5.20 (dd, *J* = 17.4, 1.1 Hz, 1 H, =CH_2), 5.93 (dd, *J* = 17.4, 10.8 Hz, 1 H, -CH=).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.7 (19-$COOCH_3$), 146.7 (C-14), 111.4 (C-15), 77.1 (C-8), 74.4 (C-13), 63.2 (C-17), 56.9* (C-9), 51.4* (C-5), 51.3 (19-COOMe), 43.8 (C-4), 40.0 (C-1), 38.1 (C-3), 37.8 (C-10), 37.7 (C-6), 33.0 (C-12), 30.0 (C-14), 28.6 (C-18), 21.5 (C-7), 19.1 (C-2), 15.1 (C-11), 13.0 (C-20).