Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1459–1462

TETRAHEDRON:
ASYMMETRY

A novel rearrangement of eudesmanolide enol ester epoxide: facile 1-step construction of the salvialane sesquiterpene skeleton

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Received 28 April 2001; accepted 31 May 2001

Abstract—A novel carbon–carbon rearrangement for the eudesmanolide sesquiterpene enol ester epoxide in the presence of a catalytic amount of Lewis acids (3–10 mol%) or an excess of NaOMe is disclosed. This reaction was developed to give a facile, one-step procedure for the construction of naturally occurring and bioactive salvialane sesquiterpenes. The reaction conditions were investigated extensively and a possible reaction mechanism is also discussed. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The enol ester epoxide is a very important class of building block in organic synthesis and the Lewis acid-catalyzed stereoselective rearrangements of these compounds has attracted great interest.[1,2] However, carbon–carbon rearrangements involving this structural moiety have not been reported to date. Recently, we have found that a fully substituted enol ester epoxide **3** with the eudesmanolide sesquiterpene skeleton could undergo a novel stereoselective Lewis acid-catalyzed or base-mediated carbon–carbon rearrangement to form the α-keto ester or α-keto alcohol products **6** and **10**, respectively. The synthetic value of this reaction lies in the resultant facile construction of the naturally occurring and bioactive salvialane sesquiterpene skeleton,[3] and other biologically important terpenoids incorporating the fused cyclopentane units bearing *syn*-methyl and *iso*-propyl groups. These structures are generally difficult to access in organic synthesis.[4–6] The facility and high stereoselectivity of this reaction suggests that the salvialane sesquiterpene is bio-generated more easily from eudesmanolide sesquiterpene.[7]

2. Results and discussion

Our study started from the naturally abundant and synthetically versatile α-santonin **1**.[8] The key epoxide **3** was prepared from **1** through three steps (Scheme 1) and characterized by NMR spectroscopy. The stereochemical assignment of the α-epoxy function in **3** was based on the consideration that there exists the β-C(4), C(10) and C(7) groups around the C(5)–C(6) double bond in **2**. Initial treatment of **3** with $ZnBr_2$ (10 mol%) in CH_2Cl_2 at ambient temperature for 12 hours readily afforded the α-keto ester **6** as the only product in 87% yield, whose structure and stereochemistry were characterized by NMR and mass spectroscopy and further confirmed by X-ray diffraction (Fig. 1). A series of Lewis acids have been subjected to examination and the results are presented in Table 1. It is notable that most examples (entries 1–9) in Table 1 gave good to high yields as well as excellent stereoselectivity with reasonable reaction times. We were unable to isolate any other diastereoisomers of **6** in these above examples. In entries 10–12, however, the reaction systems generally produced the additional (unidentified) side products. In addition, weaker Lewis acids (e.g. $Pd(OAc)_2$, $Hg(OAc)_2$, $HgCl_2$ and $MgBr_2$) proved to be ineffective in this reaction and protonic acids gave complex mixtures of products.

It is possible that the reaction process involved initial coordination–activation between the Lewis acid and the epoxide of **3**,[2a] which then led to epoxide ring-opening and the formation of a C(6)-cation transition state **4**. As the acyl group was bonded to the lactone ring, the step following ring-opening would be the attack on C(6) by C(10), which leads to the C(5)-keto–C(6)-ester product **6** after elimination of the Lewis acid. This contrasts with the reported acyl group shift from C(6)–O to C(5)–O, which leads to a C(6)-keto–C(5)-ester product.[2a] The stereochemistry of C(6), as deter-

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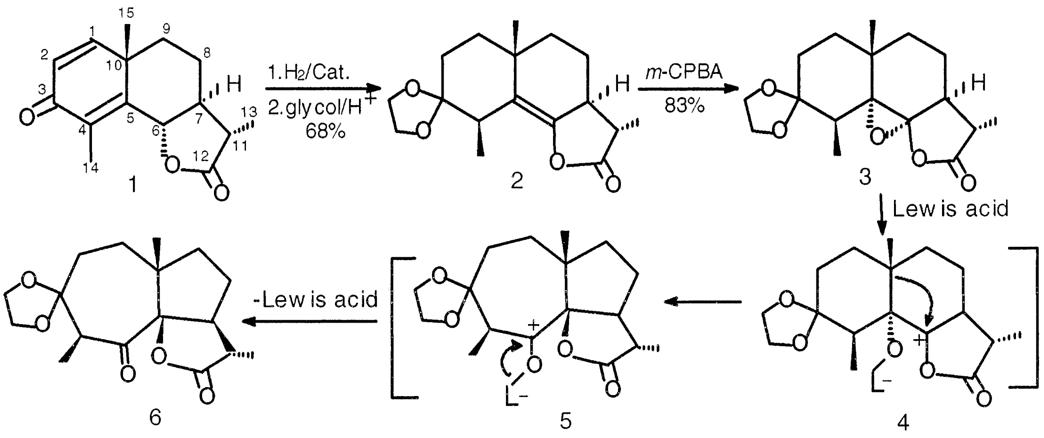
PII: S0957-4166(01)00255-5



Scheme 1.

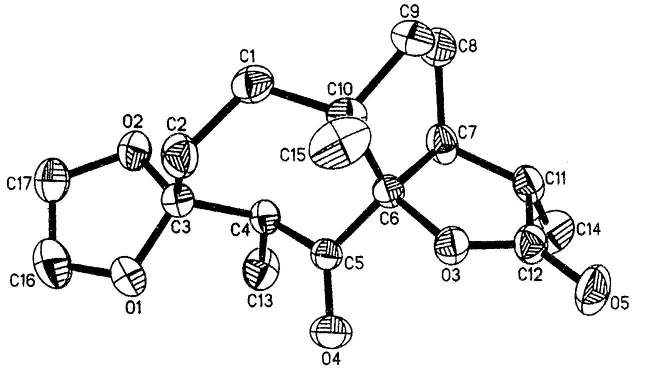


Figure 1. X-Ray structure of compound **6**.

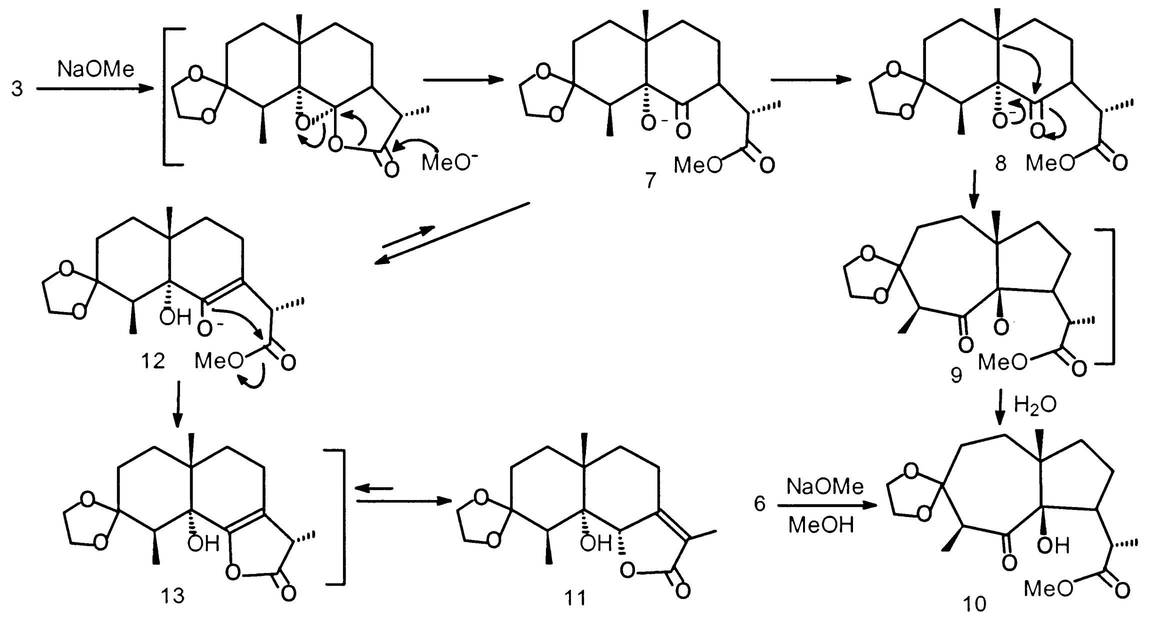
mined by X-ray diffraction analysis, suggested the epoxy ring-opening and the accompanying C(10)-shift is similar to a cooperative S_N2 process.

The second aspect of our study focussed on the base-promoted rearrangement of **3**. Initially we treated an ethereal solution of **3** with 5 equivalents of NaOMe at ambient temperature and obtained, after aqueous workup, a mixture of the C(5)-keto–C(6)-hydroxy ester product **10** and the δ-butenolide lactone product **11** in a ratio of 62:38 (Scheme 2). The structure and stereochemistry of **10** were determined by spectroscopy and by matching with the ring opening-methoxylation product (obtained from the established compound **6** in 95% yield). Also the structure of **11** was determined by spectroscopy and the stereochemistry at C(6) was confirmed by 2D-NOE NMR techniques. Further investigation showed that this base-promoted rearrangement was dependent on the nature of the solvent. Therefore, various solvent systems were examined and the results are shown in Table 2.

It is interesting to note that if the reaction was completed in ether solvents (entries 1–3), it afforded mainly **10**, with the reaction in DME giving the highest ratio (73/27) of **10**/**11**. If the reaction was completed in solvents which are completely miscible with water, however, it gave mainly **11** (entries 4 and 5) and completing the reactions in acetone or methanol gave **11** as the only product (entries 6 and 7). Unfortunately, we could not obtain **10** as the sole product even after screening a variety of solvents. In all examples of Table 2, we were unable to isolate any diastereoisomers of **10**. But carefully quenching the reaction system in entry 1 with an excess of saturated aqueous NH_4Cl solution a few minutes after the start of the reaction afforded the ketone derived from intermediate **7** in 85% yield.

Table 1. Reaction of epoxide **3** with Lewis acid catalysts

Entry	Lewis acid (mol%)	Solvent	Time (h)	Temp.	Isolated yield (%)
1	$PdCl_2$ (10)	CH_2Cl_2	13	rt	98
2	$AlCl_3$ (3)	CH_2Cl_2	18	rt	92
3	$SnCl_4$ (3)	C_6H_6	1	rt	91
4	$AlBr_3$ (5)	CH_2Cl_2	21	rt	91
5	$ZnBr_2$ (10)	CH_2Cl_2	13	rt	87
6	$BF_3{\cdot}OEt_2$ (3)	CH_2Cl_2	6	rt	83
7	$Ti(O^iPr)_2Cl_2$ (5)	CH_2Cl_2	21	rt	80
8	$Sn(OTf)_2$ (5)	CH_2Cl_2	4	rt	78
9	$SnCl_2$ (5)	CH_2Cl_2	10	rt	67
10	SmI_2 (5)	C_6H_6	12	Reflux	57
11	$ZnCl_2$ (10)	CH_2Cl_2	9	Reflux	44
12	$TiCl_4$ (3)	CH_2Cl_2	5	rt	34



Scheme 2.

Table 2. Reaction of epoxide **3** with NaOMe (5 equiv.) in various solvents

Entry	Solvent	Time (h)	Ratio of **10**/**11**	Isolated yield (%)
1	Et_2O	0.5	62:38	99
2	THF	0.5	69:31	96
3	DME	0.5	73:27	93
4	DMF	0.5	32:68	93
5	DMSO	0.5	23:77	86
6	Acetone	0.5	0:100	100
7	MeOH	0.5	0:100	91

Based on the above evidence, a possible mechanism was proposed as shown in Scheme 2. The initial nucleophilic addition of methoxide ion to the lactone carbonyl of **3** effects ring-opening of the lactone and then the epoxide and leads to the C(5)-hydroxy–C(6)-keto intermediate **7**, which could undergo reaction by two possible pathways to form the final products **10** and **11**. If the reaction is completed in polar solvents which are completely miscible with water (entries 4–7), the high concentration of the base (NaOMe) favors enolization of ketone **7** and therefore formation of intermediate **12**, which can then undergo intramolecular transesterification and a double bond shift to form **11**. However, if the reaction is completed in ether, in which NaOMe is less soluble, (entries 1–3), a suspension forms and the actual concentration of NaOMe in the reaction is not high enough to effect complete enolization of the ketone **7**. Therefore, a carbon–carbon migration–addition occurs which leads to **10** after aqueous workup.

In conclusion, we have reported a novel carbon–carbon rearrangement reaction, which represents a new and facile synthetic procedure for the construction of the salvialane sesquiterpene skeleton as well as the key fused cyclopentane unit bearing *syn*-methyl and *iso*-propyl. Further synthetic work using this procedure is in progress.

3. Experimental

3.1. General

The ^{1}H NMR, ^{13}C NMR and DEPT data were recorded in $CDCl_3$ solution with Brucker AM-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or $CDCl_3$. Optical rotations were determined on a JASCO J-20C polarimeter with a 0.2 dm tube. GC-MS, MS and HRMS data were measured with EI (70 eV) or FAB techniques. Column chromatographs were generally performed on silica gel (200–300 mesh) eluting with petroleum ether and EtOAc.

3.2. General procedure for the synthesis of 6

To a solution of **3** (200 mg, 0.65 mmol) in anhydrous CH_2Cl_2 or benzene (4 mL) was added Lewis acids (3–10 mol%), and the mixture was stirred at rt or reflux for 1–21 h (the starting material disappeared, checked with TLC), workup as the general procedure to afford **6** in the yield 34–98%. $[\alpha]_D^{25} = -91$ (*c* 0.01, $CHCl_3$); ^{1}H NMR: 3.97–3.81 (m, 4H), 3.50 (q, *J* 9.8 Hz, 1H), 2.87–2.85 (m, 1H), 2.40–2.47 (m, 2H), 1.99–1.87 (m, 2H), 1.78–1.71 (m, 3H), 1.58–1.50 (m, 2H), 1.09 (d, *J* 10.8 Hz, 3H), 1.02 (d, *J* 7.8 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR: 205.9, 179.0, 109.5, 101.1, 66.6, 64.8, 52.3, 50.3, 47.8, 43.6, 40.2, 33.8, 32.2, 32.0, 23.2, 17.9, 10.0; MS, *m*/*z* (%): 308 [M^+, 91], 280(8), 251(34), 195(38), 155(11), 139(10), 99(100); HRMS for $C_{17}H_{24}O_5$: calcd 308.3695, found 308.3683.

3.3. General procedure for synthesis of 10

To a solution of **3** (40 mg, 0.13 mmol) in the appropriate anhydrous solvent (1 mL) was added NaOMe (35 mg, 0.65 mmol) and the mixture was stirred at rt for 0.5 h. The reaction workup was as described in the general procedure to afford **10**. $[\alpha]_D^{25} = -89$ (*c* 0.01, $CHCl_3$); ^1H NMR: 4.10–3.82 (m, 4H), 3.67 (s, 3H), 3.02–2.95 (m, 1H), 2.59 (q, *J* 6.7 Hz, 1H), 2.40 (dt, *J* 4, 12 Hz, 1H), 2.11 (m, 1H), 1.95–1.72 (m, 4H), 1.57–1.51 (m, 1H), 1.34–1.30 (m, 2H), 1.17 (d, *J* 7.3 Hz, 3H), 0.76 (s, 3H), 0.74 (d, *J* 6.7 Hz, 3H); ^{13}C NMR: 213.0, 176.2, 109.6, 83.9, 65.8, 64.3, 51.7, 47.5, 43.0, 41.0, 39.3, 33.2, 31.2, 30.6, 26.0, 21.7, 14.8, 6.5; FAB-MS, *m*/*z* (%): 363 [M^++Na, 28], 349(37), 323(96), 184(23), 133(91), 87(100), 56(68); FAB-HRMS for $C_{18}H_{28}O_6$: calcd 340.1886, found 340.1875.

3.4. Conversion of compound 6 to 10

To a solution of **6** (100 mg, 0.32 mmol) in methanol (2 mL) was added NaOMe (10 mg), then the mixture was stirred at rt for 4 h, workup was as described in the general procedure to afford **10** (105mg, 95%).

Acknowledgements

We are grateful for financial support from NSFC (Nos. 29972019, 29925205 and QT program), FUKTME of China, the Yung Teachers' Found of Ministry of Education and the Found of Ministry of Education (No. 99209).

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