A stereoselective construction of a bicyclo[*m.n.*1] ring system from enol-lactones

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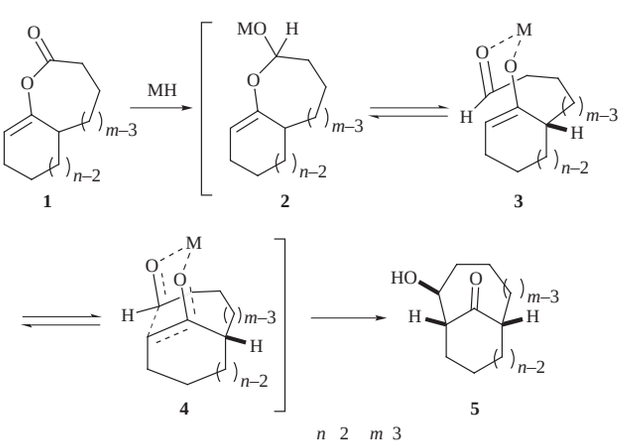
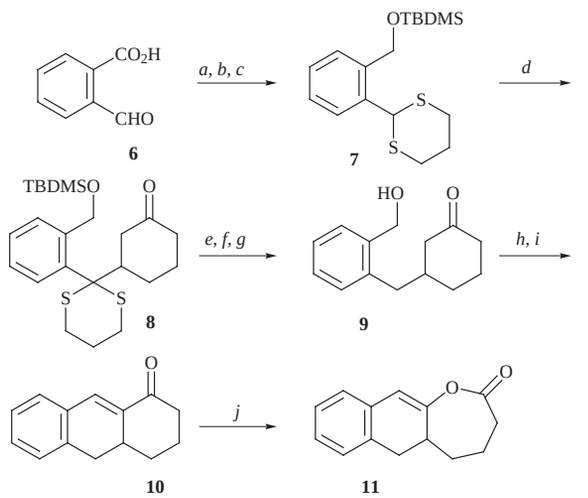
A stereoselective one-pot transformation of simple enol-lactone derivatives into the corresponding more complex compounds having the bicyclo[*m.n.*1] ring system was investigated. Under improved reduction conditions using DIBAL-H, the enol-lactones efficiently provided the bicyclo[*m.n.*1] derivatives *via* tandem reduction of the lactone moiety, aldol reaction and subsequent reduction of the resulting carbonyl functionality.

The bicyclo[*m.n.*1] ring system has been found to be a core skeleton of many natural compounds such as Taxol,[1] crispolide[2] and utilin B.[3] The development of an efficient and stereoselective method for construction of the bicyclo[*m.n.*1] ring system, therefore, would be an important theme for organic as well as medicinal chemistry. We envisioned, on the basis of literature precedents,[4,5] that simple enol-lactone derivatives like **1** would be easily transformed into the corresponding more complex bicyclo[*m.n.*1]ones **5** on the basis of the following scheme: the lactone moiety of **1** would be reduced to the lactol **2** when exposed to a suitable reducing agent. The lactol derivative **2** thus formed would be in an equilibrium with the aldehyde–enolate species **3** through C–O bond cleavage. The aldehyde–enolate derivative **3** can be regarded as a well-recognized intermediate leading to the final product **5** in the aldol reaction where the Lewis acidic metal (M) should be coordinated with both oxygen atoms of the enolate and aldehyde moieties. The reaction would be anticipated to proceed *via* the six-membered chair-like transition state[6] such as **4** resulting in the stereoselective formation of **5** with the stereochemistry depicted in Scheme 1. In this paper, we describe preliminary results on this successful conversion, as shown in Scheme 1.



Scheme 1

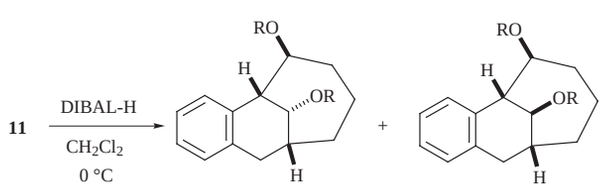
For the initial evaluation of this strategy, the enol-lactone **11** was prepared in several straightforward steps from 2-carboxybenzaldehyde **6** (Scheme 2). Protection of the aldehyde moiety of **6** with propane-1,3-dithiol was followed by reduction with lithium aluminum hydride (LAH) and protection of the resulting primary hydroxy group with a *tert*-butyldimethylsilyl



Scheme 2 *Reagents and conditions*: *a*, propane-1,3-dithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; *b*, LAH, THF, rt; *c*, TBDMSCl, imidazole, DMF, rt, 73%; *d*, LDA, cyclohexenone, THF, −78→0 °C, 73%; *e*, Raney–Ni (W-2), EtOH, reflux, *f*, $Py{\cdot}SO_3$, Et_3N, DMSO, rt; *g*, TBAF, THF, rt, 48%; *h*, PDC, CH_2Cl_2, rt; *i*, 10% NaOH aq., MeOH, 74%; *j*, *m*CPBA, CH_2Cl_2, rt, 68%.

(TBDMS) group to afford **7**. The Michael reaction[7] between **7** and cyclohexenone was carried out under the standard conditions to give **8**, which was converted into **9** by successive exposure to Raney–Ni,[8] oxidation with pyridine–sulfur trioxide and DMSO,[9] and desilylation. Oxidation of **9** with PDC gave the corresponding aldehyde, whose aldol reaction with 10% sodium hydroxide provided **10**. Treatment of **10** with *m*CPBA furnished the required enol-lactone **11**.

The first attempt at the transformation of **11** into the corresponding 8,9-benzobicyclo[4.3.1]dec-8-ene derivative was made using diisobutylaluminum hydride (DIBAL-H) as a reducing agent. Upon treatment with DIBAL-H (3 equiv.) in Et_2O at −78 °C, **11** underwent consecutive reduction of the lactone moiety, aldol reaction, and reduction of the resulting carbonyl functionality leading to the formation of **12** in 37% yield along with its isomer **13** (13%) (Scheme 3). Although the total yield



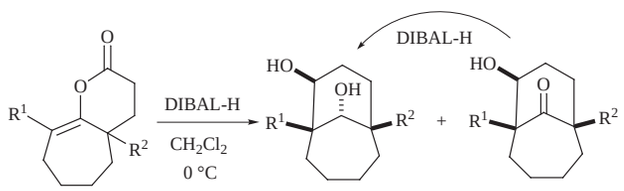
12 : R = H (81%) **13** : R = H (4%)
14 : R = Ac **15** : R = Ac
16 : R = *p*-Br-C_6H_4CO

Scheme 3

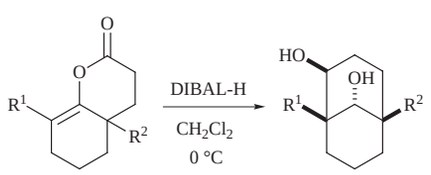
(50%) and stereoselectivity were rather lower, transformation of the simpler **11** into the more complex **12** and **13** could be attained in one operation. When this reaction was conducted in

CH_2Cl_2 at 0 °C instead of in Et_2O at −78 °C, **11** produced **12** in 81% yield in a highly stereoselective manner (**13** was obtained in 4% yield).[10] A similar result [**12** (73%) and **13** (4%)] was obtained on exposure of **11** to DIBAL-H in CH_2Cl_2 in the presence of $ZnCl_2$.[11] Other Lewis acidic metal hydride reagents like BH_3·THF, BH_3·SMe_2 and 9-BBN were also employed for this transformation, but no improvement in yield or stereoselectivity could be achieved.[12] The structure of these compounds was determined on the basis of the spectral data of **12** and **13** as well as their diacetyl derivatives **14** and **15**. In particular, the stereochemical outcome was unambiguously established as described in Scheme 3 by X-ray crystallographic analysis of the bis-*p*-bromobenzoate **16**[13] derived from **12**.

The next phase of our study now involved the application of these conditions (3 equiv. of DIBAL-H, CH_2Cl_2) to other enol-lactone derivatives. Treatment of the enol-lactone **17**[14] with DIBAL-H in CH_2Cl_2 at 0 °C gave stereoselectively the bicyclo[4.3.1]decane-7,10-diol **20** in 55% yield (Scheme 4). In



17 : $R^1 = R^2 = H$ **20** : $R^1 = R^2 = H$ **21** : $R^1 = R^2 = H$
18 : $R^1 = H, R^2 = Me$ **22** : $R^1 = H, R^2 = Me$ **23** : $R^1 = H, R^2 = Me$
19 : $R^1 = Me, R^2 = H$ **24** : $R^1 = Me, R^2 = H$ **25** : $R^1 = Me, R^2 = H$



26 : $R^1 = R^2 = H$ **27** : $R^1 = R^2 = H$
28 : $R^1 = H, R^2 = Me$ **29** : $R^1 = H, R^2 = Me$
30 : $R^1 = Me, R^2 = H$ **31** : $R^1 = Me, R^2 = H$

Scheme 4

this case, the 10-oxo derivative **21**, presumably a precursor of **20**, could be isolated in 26% yield. The conversion of **21** to **20** was easily realized by DIBAL-H reduction. Similar results were obtained when the methyl congeners **18** and **19**[14] were submitted to the reduction conditions to afford the corresponding diols **22** (44%) and **24** (53%) together with the 10-oxo derivatives **23** (38%) and **25** (41%), respectively. In addition, the exclusive formation of the bicyclo[3.3.1]nonane-2,9-diol skeleton[15] was established using the previous procedure: thus, **27** (67%), **29** (78%) and **31** (70%) were obtained as the sole products when **26**, **28** and **30**,[14] respectively, were exposed to DIBAL-H in CH_2Cl_2 at 0 °C.

In conclusion, we have improved on a method for the stereoselective construction of bicyclo[4.3.1]decane-7,10-diol derivatives and bicyclo[3.3.1]nonane-2,9-diol from the corresponding enol-lactones by simple treatment with DIBAL-H in CH_2Cl_2. Further studies in line with this program are now in progress.

Experimental

Typical method for transformation of the enol-lactone 11 into the bicyclo[4.3.1] derivative 12

To a solution of **11** (81.0 mg, 0.38 mmol) in CH_2Cl_2 (4.0 cm^3) was added DIBAL-H in hexane (1.00 mol dm^{-3}; 0.95 cm^3, 0.95 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2 h and quenched by addition of water. The reaction mixture was diluted with ethyl acetate, and washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (5:1) afforded **12** (67.2 mg, 81%) and **13** (3.4 mg, 4%). Compound **12** was converted to the corresponding acetate **14** for detailed analysis: the acetate **14** was a colourless oil (Found: C, 70.9; H, 7.4. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%); ν_{max}/cm^{-1} 1725 (CO); δ_H 7.53 (1H, d, *J* 7.5, aromatic H), 7.18 (1H, apparent t, *J* 7.5, aromatic H), 7.11 (1H, apparent t, *J* 7.5, aromatic H), 7.02 (1H, d, *J* 7.5, aromatic H), 5.42 (1H, dd, *J* 5.0, 7.0, 10-H), 5.34 (1H, apparent t, *J* 9.0, 2-H), 3.77 (1H, d, *J* 7.0, 1-H), 3.24 (1H, dd, *J* 7.5, 17.5, 7-H), 2.75 (1H, d, *J* 17.5, 7-H), 2.49 (1H, m, 6-H), 2.20–2.02 (2H, m), 2.17 (3H, s, Ac), 2.06 (3H, s, Ac), 1.92–1.85 (1H, m), 1.82–1.78 (1H, m), 1.50–1.44 (1H, m) and 1.19–1.11 (1H, m); δ_C 170.5, 170.4, 136.3, 135.0, 130.2, 128.9, 126.6, 126.3, 79.7, 74.4, 43.7, 36.4, 34.6, 34.0, 33.2, 29.7, 21.4 and 20.1; CI-MS *m*/*z* 303 ($M^+ + 1$, 1.1%), 243 (100) and 183 (16).

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12 LAH was found not to be a suitable reducing agent (see ref. 5).
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14 The starting enol-lactones were prepared according to the literature precedents (see ref. 5).
15 The corresponding 9-oxo derivatives could never be detected in more than trace quantities.

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