Functionalization of Fused Cyclopentane Derivatives using Hypervalent Iodine Reagents†

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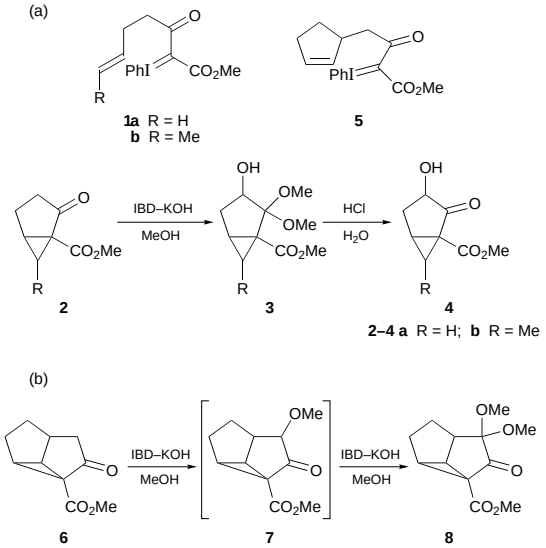
Fused cyclopentane derivatives, *viz.* methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**2a**), methyl 6-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate (**2b**) and methyl 3-oxotricyclo[3.3.0.0^{2,8}]octane-2-carboxylate (**6**), have been functionalized by using the hypervalent iodine reagents iodobenzene diacetate (IBD) and [hydroxy(tosyloxy)iodo]benzene (HTIB).

Considerable attention has been devoted to the development of methods for the synthesis and functionalization of fused cyclopentane derivatives because of the presence of this ring system in a large number of biologically active natural products.[1,2] As part of our programme on the synthetic utility of hypervalent iodine reagents, we have earlier reported a useful approach for intramolecular cyclopropanation.[3,4] This methodology, involving copper(I)-catalysed decomposition of iodonium ylides, has led to the synthesis of various bicyclic and tricyclic compounds containing a cyclopentane ring. In this paper we describe the application of hypervalent iodine reagents to the functionalization of fused bi- and tricyclopentane derivatives, *viz.* methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate (**2a**), methyl 6-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate (**2b**) and methyl 3-oxotricyclo[3.3.0.0^{2,8}]-octane-2-carboxylate (**6**).

The cyclic oxo esters **2a**, **2b** and **6**, synthesized by copper(I)-catalysed intramolecular cyclization of the respective iodonium ylides **1a**, **1b** and **5**,[3] were first subjected to oxidation with iodobenzene diacetate (IBD) in methanolic potassium hydroxide. This system (IBD–KOH/MeOH) is employed to introduce a hydroxy group at the α-position of an enolizable ketone *via* α-hydroxy dimethyl acetal formation.[5] In the present study, oxidation of bicyclic ketones **2a** and **2b** with IBD (1 mol equivalent) in KOH–MeOH afforded the normal α-hydroxy dimethyl acetals **3a** and **3b**, but no indication of the formation of such a product was observed in the oxidation of the tricyclic ketone **6** (Scheme 1a). Instead, this reaction led to the formation of the α,α-dimethoxy ketone **8** in about 35% yield (Scheme 1b). The formation of product **8** occurs *via* the intermediate **7**. As expected, treatment of **6** with 2 mol equivalents of IBD gave **8** in optimum yield (77%).

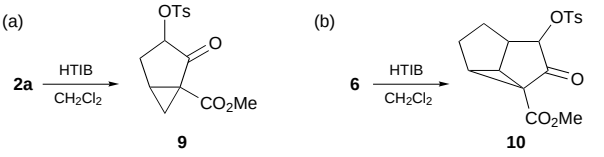


Scheme 1

Keeping in mind that methyl 3-hydroxy-2-oxobicyclo-[3.1.0]hexane-1-carboxylate (**4a**) could be used as a ring A synthon in vitamin D synthesis,[6] it was considered worthwhile to hydrolyse the acetals **3a** and **3b** to **4a** and **4b** respectively. Thus, **3a** and **3b** were treated with dilute hydrochloric acid to obtain the corresponding α-hydroxyketones (**4a** and **4b**).

We then turned our attention to effecting α-tosyloxylation of the ketones **2a** and **6** with [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent). The method of Koser *et al.*[7,8] successfully transformed these ketones into the corresponding α-tosyloxy ketones **9** and **10** (Scheme 2a and b).

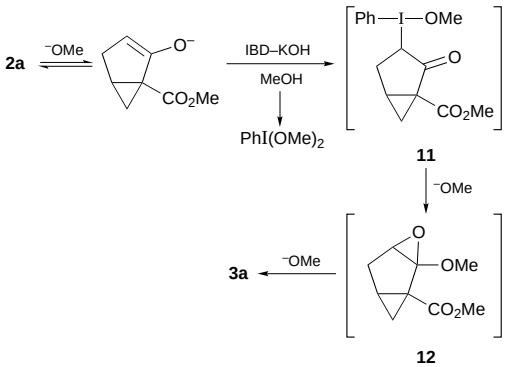
The observed difference in the reactivity pattern of the bicyclic and tricyclic ketones towards IBD–KOH/MeOH



Scheme 2

may be rationalized on the basis of steric factors involved in the mechanistic pathway. The first step in the iodine(III)-mediated α-hydroxy dimethyl acetal formation is the creation of an electrophilic centre α to the carbonyl group by addition of the hypervalent iodine species $PhI(OMe)_2$ [generated from IBD–KOH/MeOH] to give an I^{III} intermediate (*e.g.*, **11** from **2a**). The fate of this intermediate is controlled both by the reaction conditions as well as its chemical structure. In the presence of KOH–MeOH, formation of an α-hydroxy dimethyl acetal occurs by nucleophilic attack of methoxide ion in two steps: initial attack of $^-$OMe at the carbonyl group gives epoxide **12**, which subsequently undergoes ring opening by the second attack of $^-$OMe to yield the product (**3a** starting from **2a**; Scheme 3).

The tricyclic ketone **6** does not follow the normal pathway, presumably because of the steric hindrance associated with



Scheme 3

*To receive any correspondence.
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.
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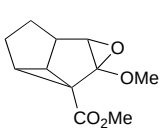

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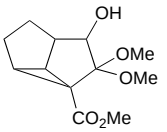

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the epoxide **13** which is prerequisite for the formation of the desired α-hydroxy dimethyl acetal **14**.[5] In this case the I^{III} intermediate (analogous to **11**) undergoes nucleophilic substitution by methoxide ion followed by further oxidation of the resultant α-methoxy ketone **7** to yield the α,α-dimethoxy ketone **8**.

The formation of the α-toxyloxy ketones **9** and **10** occurs according to the general pathway for α-tosyloxylation of ketones.[7,8]

Finally, noteworthy features of this study are: (i) several new α-functionalized ketones containing bicyclo[3.1.0]hexane and tricyclo[3.3.0.$0^{2,8}$]octane systems are easily accessible; (ii) reaction conditions employed for these α-functionalizations do not affect the cyclopropane system of the ketones **2a**, **2b** or **6**; (iii) it is demonstrated that hypervalent oxidative α-hydroxylation of ketones using IBD–KOH/MeOH is applicable to the [3.1.0]bicyclic ketones **2a** and **2b**, but that the ketone **6**, which contains the tricyclo[3.3.0.$0^{2,8}$]octane system, leads to an α,α-dimethoxylated ketone; and (iv) the HTIB-induced method works successfully to introduce a tosyloxy group at the α-position for both bicyclic and tricyclic ketones.

Experimental

Mps and bps are uncorrected. Silica gel (230–400 mesh) was used for column chromatography.

The cyclic ketones **2a**, **2b** and **6** were prepared according to our previous method involving copper(I)-catalysed decomposition of the corresponding iodonium ylides **1a**, **1b** and **5**, which in turn were prepared from the reaction of appropriate β-oxo esters with IBD–KOH/MeOH.[3]

Conversion of Methyl 2-*Oxobicyclo*[3.1.0]*hexane*-1-*carboxylate* (**2a**) *into Methyl* 3-*Hydroxy*-2-*oxobicyclo*[3.1.0]*hexane*-1-*carboxylate* (**4a**).—*Step 1. Methyl* 3-*hydroxy*-2,2-*dimethoxybicyclo*[3.1.0]*hexane*-1-*carboxylate* (**3a**). To a stirred solution of potassium hydroxide (1.68 g, 30 mmol) in methanol (40 ml) at 0 °C was added a solution of the ketone **2a** (1.54 g, 10 mmol) in methanol (10 ml) over 10 min. The solution was stirred for another 10 min and then iodobenzene diacetate (3.54 g, 11 mmol) was added in three portions over 10 min. The resulting homogenous mixture was stirred for 2 h at 0 °C and then for 2 h at room temperature, concentrated *in vacuo*, diluted with water (40 ml) and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to remove solvent and iodobenzene. The crude hydroxy dimethyl acetal **3a** (1.60 g), obtained as an oil [ν_{max}/cm^{-1} (neat) 3505, 1725; δ_H (400 MHz, $CDCl_3$) 1.35 (m, 1 H), 1.48 (t, *J* 5.5 Hz, 1 H), 1.76 (d, *J* 14 Hz, 1 H), 2.07 (m, 1 H), 2.24 (m, 1 H), 3.29 (s, 3 H), 3.59 (s, 3 H), 3.62 (s, 3 H), 4.01 (d, *J* 7.0 Hz, 1 H). δ_C (100 MHz, $CDCl_3$) 16.87, 26.88, 31.84, 34.454, 59.26, 51.39, 53.04, 73.43, 108.21, 171.10; *m*/*z* (CI) 217 (M + 1, 1.4%), 199 (3), 185 (51), 1543 (100)], was used as such for the next step.

Step 2. Methyl 3-*hydroxy*-2-*oxobicyclo*[3.1.0]*hexane*-1-*carboxylate* (**4a**). To a solution of the crude dimethyl acetal **3a** (1.5 g) in methanol (10 ml) was added 2 M HCl (10 ml) and the homogeneous mixture was allowed to stir at room temperature for 3 h. Methanol was removed *in vacuo* and the aqueous mixture was extracted with dichloromethane (4 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the resulting residual mass was purified by flash column chromatography on silica gel eluting with hexanes–diethyl ether (1:1 v/v) to give 0.5 g (42%) of **4a** as an *oil*, ν_{max}/cm^{-1} (neat) 3463, 1757, 1722; δ_H (300 MHz, $CDCl_3$) 0.84 (d, *J* 5.5 Hz, 1 H), 1.69–1.74 (m, 1 H), 2.16–2.22 (m, 1 H), 2.40 (d, *J* 18 Hz, 1 H), 2.78 (d, *J* 2.7 Hz, 1 H), 2.83–2.91 (m, 1 H), 3.76 (s, 3 H), 5.01 (s, 1 H); δ_C (75.43 MHz, $CDCl_3$) 17.87, 21.28, 30.90, 38.38, 52.37, 75.02, 172.70, 211.82; *m*/*z* (CI) 171 (M + 1, 31%), 153 (100), 139 (22) (Found: C, 55.86; H, 5.99. $C_8H_{10}O_4$ requires C, 56.47; H, 5.88%).

Conversion of **2b** into **4b** was also effected according to the above method. **3b**: *oil*; yield 51%; ν_{max}/cm^{-1} (neat) 3521, 1732; δ_H (300 MHz, $CDCl_3$) 1.03 (d, *J* 6.3 Hz, 3 H), 1.33–1.48 (m, 2 H), 1.64 (t, 1 H), 2.32–2.43 (m, 1 H), 2.62 (br d, 1 H), 3.27 (s, 3 H), 3.53 (s, 3 H), 3.67 (s, 3 H), 4.10 (m, 1 H); δ_C (75.43 MHz, $CDCl_3$) 13.37, 25.35, 28.20, 29.59, 33.69, 42.46, 49.99, 51.57, 51.77, 76.98, 107.60; *m*/*z* (CI) 231 (M + 1, 11%), 213 (23), 199 (30), 185 (74), 167 (90), 153 (100), 135 (45) (Found: C, 58.13; H, 7.50. $C_{11}H_{18}O_5$ requires C, 57.39; H, 7.83%). **4b**: *oil*; ν_{max}/cm^{-1} (neat) 1754, 1723; δ_H (300 MHz, $CDCl_3$) 1.18–1.23 (m, 1 H), 1.31 (d, *J* 6.0 Hz, 3 H), 2.05 (t, *J* 5.4 Hz, 1 H), 2.42 (d, *J* 18 Hz, 1 H), 2.76–2.88 (m, 2 H), 3.79 (s, 3 H, 4.83 (s, 1 H); δ_C (75.43 MHz, $CDCl_3$) 11.45, 26.59, 27.14, 35.67, 38.65, 52.16, 75.80, 171.46, 212.16; *m*/*z* (CI) (M + 1, 54%), 167 (100), 153 (58), 135 (26) (Found: C, 58.48; H, 6.74. $C_9H_{12}O_4$ requries C, 58.70; H, 6.52%).

Methyl 4,4-*Dimethoxy*-3-*oxotricyclo*[3.3.0.$0^{2,8}$]*octane*-2-*carboxylate* (**8**).—A solution of the ketone **6** (1.8 g, 10 mmol) in methanol (5 ml) was treated with KOH (3.36 g, 60 mmol) in methanol (50 ml) followed by IBD (6.44 g, 20 mmol) according to the procedure described for the conversion of **2** into **3**. The crude product was purified by flash column chromatography on silica gel, eluting with hexanes–diethyl ether (1:1) to give 1.74 g (77%) of **8** as an *oil*, ν_{max}/cm^{-1} (neat) 1733, 1717; δ_H (300 MHz, $CDCl_3$) 1.80–2.04 (m, 3 H), 2.18–2.34 (m, 2 H), 2.74–2.79 (m, 1 H), 2.85–2.92 (m, 1 H), 3.44 (s, 3 H), 3.57 (s, 3 H), 3.68 (s, 3 H); δ_C 22.93, 31.36, 33.03, 39.93, 40.29, 49.47, 50.40, 51.99, 52.82, 100.39, 169.20, 211.94; *m*/*z* (CI) 241 (M + 1, 15%), 223 (30), 209 (100) (Found: C, 59.61; H, 6.62; $C_{12}H_{16}O_5$ requires C, 60.00; H, 6.67%).

Procedure for the α-Tosyloxylation of **2** *and* **6**.—To a stirred solution of the ketone (10 mmol) in dichloromethane (30 ml) was added [hydroxy(tosyloxy)iodo]benzene (7.84 g, 20 mmol) and the mixture was refluxed overnight. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel to give the α-tosyloxy ketone as a colourless crystalline solid which was recrystallized from the appropriate solvent. *Methyl* 2-*oxo*-3-*tosyloxybicyclo*[3.1.0]*hexane*-1-*carboxylate* (**9**), yield 65%, had mp 118–119 °C; ν_{max}/cm^{-1} (KBr) 1765, 1720, 1372, 1177; δ_H (400 MHz, $CDCl_3$) 1.62 (t, *J* 5.4 Hz, 1 H), 2.08 (dd, J_1 2.6 Hz, J_2 15.1 Hz, 1 H), 2.13 (m, 1 H), 2.40 (s, 3 H), 2.50 (m, 1 H), 2.61 (m, 1 H), 3.67 (s, 3 H), 4.65 (dd, J_1 2.6 Hz, J_2 9.7 Hz, 1 H), 7.33 (d, *J* 8.1 Hz, 2 H), 7.75 (d, *J* 8.1 Hz, 2 H); δ_C (100 MHz, $CDCl_3$) 21.66, 23.67, 29.45, 29.56, 36.79, 52.53, 78.08, 128.08, 129.92, 132.85, 145.33, 167.80, 197.37; *m*/*z* (CI) 325 (M + 1, 100%), 293 (39), 169 (17), 155 (49), 153 (94) (Found: C, 55.48; H, 4.95; S, 9.87. $C_{15}H_{16}O_6S$ requires C, 55.56; H, 4.94; S, 9.88). *Methyl* 3-*oxo*-4-*tosyloxybicyclo*[3.1.0.$0^{2,8}$]*octane*-2-*carboxylate* (**10**), yield 75%, had mp 158–160 °C; ν_{max}/cm^{-1} (KBr) 1738, 1711, 1368, 1179; δ_H (400 MHz, $CDCl_3$) 1.85 (m, 1 H), 2.10–2.20 (m, 3 H), 2.38 (m, 1 H), 2.49 (s, 3 H), 2.68 (d, 1 H), 2.98 (dd, J_1 4.3 Hz, J_2 7.7 Hz, 1 H), 3.75 (s, 3 H), 5.08 (t, *J* 5.0 Hz, 1 H), 7.38 (d, *J* 8.3 Hz, 2 H), 7.80 (d, *J* 8.3 Hz, 2 H); δ_C (100 MHz, $CDCl_3$) 15.47, 21.66; 24.04, 37.47, 38.93, 44.26, 45.66, 52.49, 73.91, 127.80, 130.14, 133.33, 145.44, 166.63, 200.53; *m*/*z* (CI) 351 (M + 1, 79%), 319 (8), 179 (100) (Found: C, 57.89; H, 5.16; S, 8.84. $C_{17}H_{18}O_6S$ requires C, 58.29; H, 5.14; S, 9.14).

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