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Desymmetrisation of *meso*-methylcyclooctanones. Highly enantioselective synthesis of C_8 *syn*-isoprenoid and *syn*,*syn*-deoxypropionate subunits from a bicyclo[3.3.1]nonane precursor

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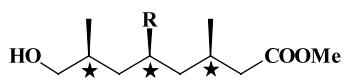
Abstract—The methyl esters of 3*R*,7*S*-dimethyl- and 3*R*,5*R*,7*S*-trimethyl-8-hydroxyoctanoic acids have been prepared in good yields and with e.e. >98% by chemical elaboration of the known *exo*,*exo*-3,7-dimethylbicyclo[3.3.1]nonan-9-one, the key step involving the desymmetrisation of the intermediate *meso*-ketones *cis*-3,7-dimethyl- and *cis*,*cis*-3,5,7-trimethyl-cyclooctanone through the corresponding chiral enolates generated by the lithium amide of the (+)bis[(*R*)-(1-phenylethylamine)]. The very high enantioselectivity observed might be related to the conformational features of the eight-membered ring.

In spite of the large amount of methods to induce chirality at hetero-functionalised carbons, little attention has been devoted to the induction of chirality at carbons carrying only alkyl substituents. However, optically active carbon chains carrying methyl groups with regio- and stereo-regular distribution (polymethyl alternating systems) are widespread in natural compounds. In particular, the *syn*-isoprenoid (1,5-dimethyl) pattern is present as sub-unit in vitamins,[1] plant metabolites,[2] insect pheromones,[3] marine natural products[4] and membrane lipids,[5] while the *syn*,*syn*-deoxypropionate (1,3,5-trimethyl) pattern is found in aggregation pheromones,[6] ionophores,[7] macrolide antibiotics[8] and in polymethylated fatty acids.[9] Moreover, chiral polymethyl alternating systems were recently receiving increasing attention as starting material in the preparation of methyl branched environmentally benign surfactants or polymethylated phospholipides used to enhance the stability of liposomial membranes.[10]

On these grounds, we focused our attention on the enantioselective synthesis of the hydroxy esters **1** and **2** as useful sub-units to be assembled for the synthesis of more complex polymethyl alternating systems present in natural compounds.



1: R=H
2: R=Me

Compound **2** is novel, while the enantioselective synthesis of **1** (3*R*,7*S*) has already been reported[11a] with high e.e., the key step being the desymmetrisation of the *meso*-*cis*-3,7-dimethylcyclooctanone **6** through a chiral enolate generated by the chiral lithium amide **9** (Scheme 1). However, in our knowledge, the very high enantioselectivity reported in that case has only a previous record for a different C_8-ring[11b] and it has neither been rationalised nor extended to other cyclooctanones. Therefore, it cannot be considered as a general trend for eight-membered cyclic ketones.

On the other hand, stereocontrolled synthesis of substituted cyclooctanones can be obtained by bridge fission of substituted bicyclo[3.3.1]nonanes,[12] where the

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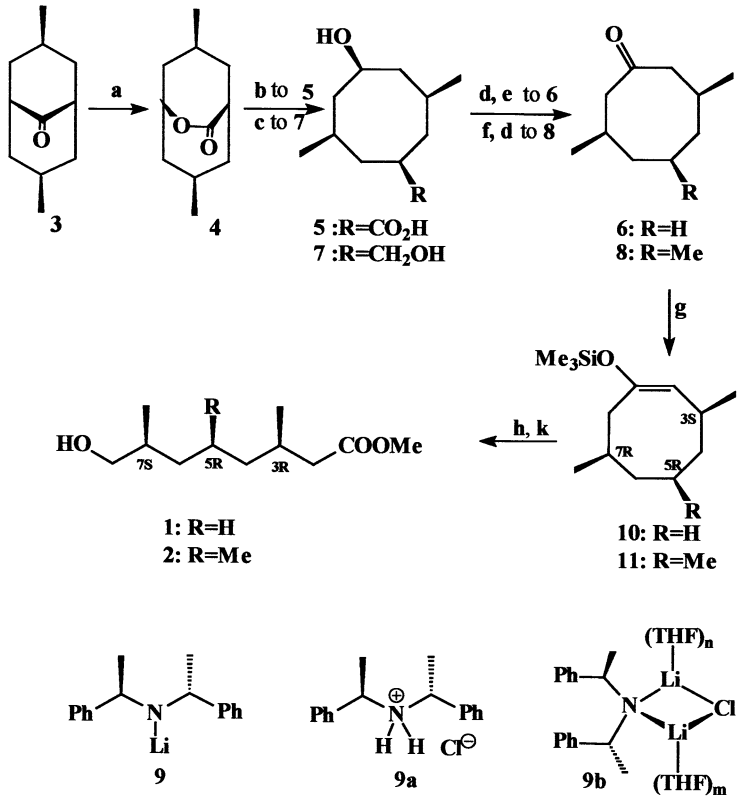


Scheme 1. (a) UHP, $(CF_3CO)_2O$, CH_2Cl_2, rt, 85%; (b) OH^-/H_2O, 98%; (c) LAH, Et_2O, rt, 98%; (d) PDC, CH_2Cl_2, rt, 85%; (e) acridine, 2% *t*BuSH, *hv*, 98% via GC; (f) Ireland's deoxygenation,[15] 87%; (g) **9a**, THF, 2BuLi, TMSCl, −78°C, 95%; (h) O_3, $MeOH/CH_2Cl_2$, −78°C then $NaBH_4$, rt, 90%; (k) MeOH/TsOH, reflux, 95%.

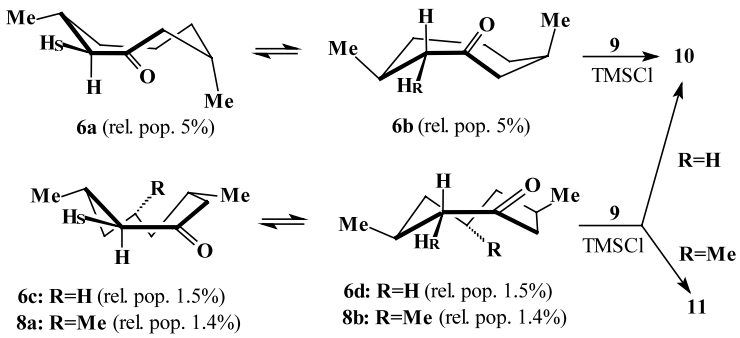
required stereochemistry can be easily installed and transferred to the final cyclooctanones. Therefore, in order both to verify the behaviour of other *meso*-cyclooctanones with the chiral lithium amide **9** and to find a versatile enantioselective route to isoprenoid and deoxypropionate C_8-synthons, we carried out the synthesis of both compounds **1** and **2** starting from the recently reported[13] *exo*,*exo*-3,7-dimethylbicyclo-[3.3.1]nonan-9-one **3** (Scheme 1).

Bridge fission of ketone **3** was obtained by Baeyer–Villiger oxidation and gave the lactone **4** as a common intermediate for both cyclooctanones **6** and **8**. Saponification of lactone **4** led to the unstable hydroxyacid **5**† that was immediately oxidised and photochemically decarboxylated,[14] to afford the volatile cyclooctanone **6**. Alternatively, LAH reduction of **4** gave the diol **7**, which was selectively deoxygenated at the primary hydroxy group by using a modified Ireland procedure[15] and oxidised to afford ketone **8**. Both the two cyclooctanones **6** and **8** were then subjected to the above reported desymmetrisation procedure.[11] The chiral lithium amide **9** was generated from the corresponding amine hydrochloride **9a** with 2 equiv.[16] of BuLi, and the produced enolates were trapped with TMSCl using the 'internal' quenching technique[17] to give the silylenol-ethers **10** and **11**. Subsequent one-pot ozonolysis–$NaBH_4$ reduction, followed by methylation of the produced hydroxyacids (not purified) gave the hydroxyesters **1**[11] and **2**[18] in high optical purity (>98% e.e. via GC on a dimethyl-pentyl-β-CDX chiral column in comparison with the racemic mixtures) and high yield (85%). All intermediate compounds showed spectroscopic properties in agreement with the reported structures.

As expected, compound **1** showed $[\alpha]_D^{25}$ −3.9, identical to the literature.[11a] This confirmed the absolute configuration of **1** to be 3*R*,7*S* and indicated an enantioselective extraction of the pro-*R* proton during the enolization process to give the intermediate silylenol-ether **10** with the 3*S*,7*R* configuration. The apparent change of configuration in the conversion of **10** to **1** is simply due to the different numbering in the two compounds.

As far as the novel ester **2** is concerned, due to the difficulty in correlating natural products, the absolute configuration was assigned by analogy with **1** on the basis of the following considerations. The enantioselectivity of deprotonation of cyclic ketones by **9**[19] depends on (i) the structure of the active deprotonating species, (ii) the structure of the transition state and (iii) the conformational requisites for proton extraction from the substrate, the first two points being still under investigation at this time. The cyclic lithium aggregate

† Due to the *cis*-configuration of the hydroxyl and carboxyl groups, **5** relactonises during workup or standing, unless temperature is kept under 0°C.



Scheme 2.

9b has been detected in THF solutions of **9** containing LiCl and proposed as the active species,[20] while an eight-membered transition state has been calculated[21] and proposed in place of the classic six-membered Ireland model.[22] However, the above findings are unable to explain the enantioselection in *meso*-cyclohexanones and in cyclooctanone **6**. On the contrary, the conformational requisites for proton extraction from the substrate can be easily obtained by molecular mechanics calculations. Enantioselective enolate formation in *meso*-cyclohexanones takes place by extraction of a single axial proton from highly populated chair *meso*-conformations,[19] while more severe conformational requisites are needed for the same process in cyclooctanones, where proton extraction can take place only if (i) the proton to be extracted is perpendicular to the carbonyl plane and (ii) the developing double bond is *cis* within the C_8-ring.[23] In our case, molecular mechanics calculations (MacroModel/BatchMin 4.5,[24] MM2, GB/SA $CHCl_3$) for the cyclooctanone **6** found 11 conformations populated at −80°C, but only the two couples of poorly populated conformational antipodes **6a**–**b** and **6c**–**d** shown in Scheme 2[‡] satisfied both the above conditions for proton extraction, namely the *pseudo*-equatorial protons marked H_S and H_R, respectively. In reality, our and previous[11] experimental results show that only the H_R protons are extracted and, therefore, only conformations **6b** and **6d** are reactive. The more severe conformational requisites for proton extraction from cyclooctanones might be related to the higher enantioselection (ca 99:1) observed in these latter when compared with cyclohexanones (ca 20:1).[25]

Extension of the same approach to ketone **8** gave the couple of conformational antipodes **8a**–**b** as the only reactive among five found conformations. Conformers **8a**–**b** are very similar to **6c**–**d** and the additional methyl group at C_5 is far and points away from the reaction centre, therefore, by analogy with **6d**, it is reasonable to assume the conformer **8b** as the only reactive at the pro-*R* proton. This allows the 3*S*,5*R*,7*R* configuration to be assigned to the silylenolether **11** and the 3*R*,5*R*,7*S* configuration to be assigned to the hydroxyester **2**. Accordingly, the latter compound shows $[\alpha]_D^{25}$ close, in sign and absolute value,[18] to that of **1** and the same GC elution order of **1** within the respective racemic mixtures.

In conclusion, the high enantioselective pro-*R* proton extraction by the chiral lithium amide **9** seems to be general in *meso*-cyclooctanones. This is likely related to the conformational features of the eight-membered ring and can be used as a key step in a versatile synthetic route from bicyclo[3.3.1]nonane derivatives to optically active isoprenoid and deoxypropionate C_8-synthons.

[‡] Bonds in **bold** in Scheme 2 show the *cis* configuration within the C_8-ring of the developing double bond.

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18. **2**: ^{1}H NMR ($CDCl_3$) δ: 3.64 (s, 3H, OCH_3), 3.50 (dd, 1H, $J=10.5$, 5.1, Hz, H_{8a}), 3.35 (dd, 1H, $J=10.5$, 6.6 Hz, H_{8b}), 2.30 (dd, 1H, $J=17.5$, 8.8 Hz, H_{2a}), 2.06 (dd, 1H, $J=17.5$, 8.3 Hz, H_{2b}), 2.00–1.00 (m, 8H), 0.90 (d, 3H, $J=6.3$ Hz, CH_3), 0.89 (d, 3H, $J=6.6$ Hz, CH_3), 0.86 (d, 3H, $J=6.5$ Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 174.07 (C_1), 68.06 (C_8), 51.29 (OCH_3), 44.41 (C_2), 41.05 (C_4), 40.09 (C_6), 32.85 (C_7), 27.68 (C_5), 27.41 (C_3), 20.52 (C_3-CH_3), 20.45 ($C_{5'}$), 17.29 ($C_{7'}$). MS (m/z,%): 216 (M^+, not detected), 186 (15), 143 (12), 129 (17), 101 (100), 83 (65), 74 (47), 69 (66). $[\alpha]_D^{25}$ −6.7 (*c* 5, $CHCl_3$).
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