An enantiospecific synthetic approach to the limonoids

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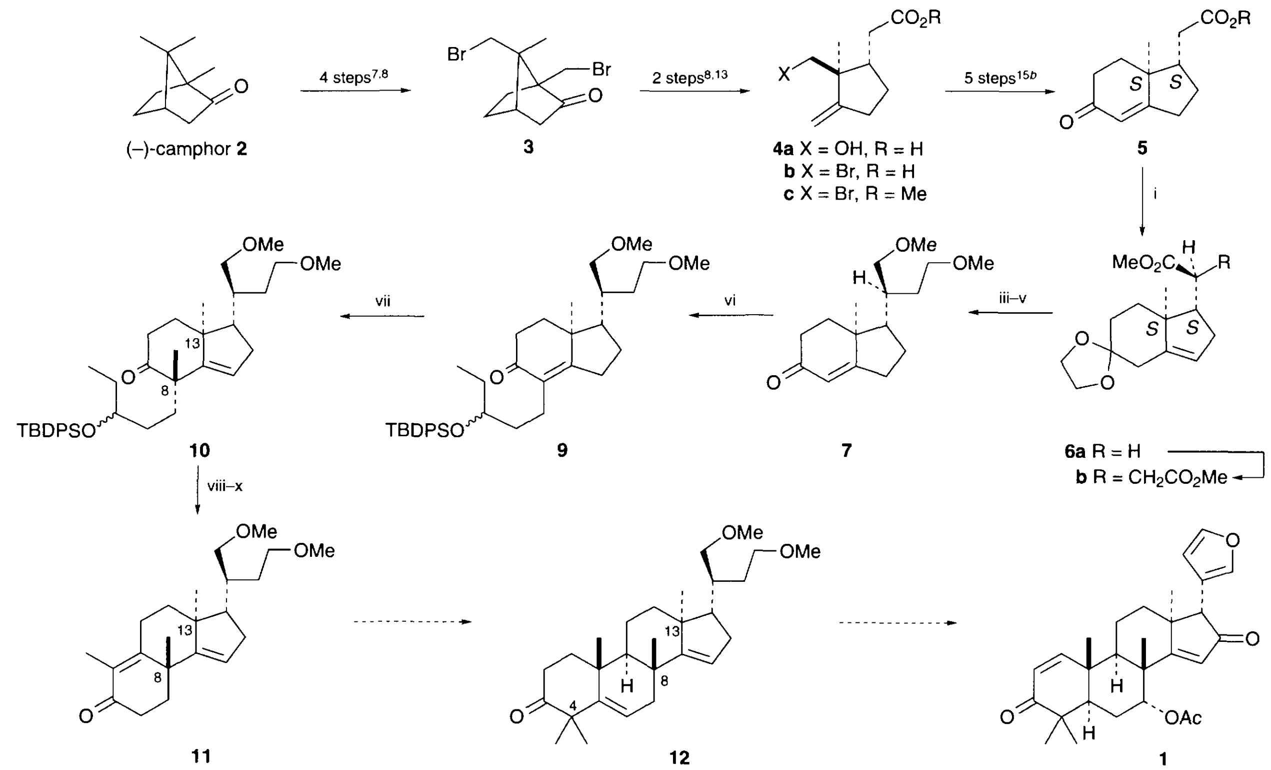
Enone-ester 5, derived from (−)-9,10-dibromocamphor 3, is converted to a tricyclic enone 11 that may be of value in an enantiospecific synthesis of the limonoids.

The limonoids[1] are a group of complex, structurally diverse tetranortriterpenoids found generally in plants belonging to the Meliaceae, Rutaceae and Cneoraceae families. Representative examples are azadiradione **1** (Scheme 1), limonin, gedunin, obacunone and azadiractin. There is considerable interest in their anti-malarial, insect anti-feedant or insecticidal properties[2–4] and this fact, coupled with their structural complexity, has stimulated interest in their total synthesis.[4–6] Corey and Hahl[5] have developed a synthetic route to (±)-azadiradione based on stereocontrolled polyalkene cyclisation, while other groups have reported[6] approaches to limonoid model C,D-ring systems.

Previous investigations in our laboratory have shown that (−)-9,10-dibromocamphor **3**, derived [7,8] from (−)-camphor **2**, undergoes efficient ring cleavage to provide monocyclic (+)-hydroxy-acid **4a**,[8] (+)-bromo-acid **4b**[8] and (+)-bromo-ester **4c**[8,13] (Scheme 1) in high yield. Later studies demonstrated the utility of **4a–c** or their enantiomers, derived from (+)-9,10-dibromocamphor, as intermediates, in terpenoid[9–12] and steroid[13–15] synthesis. As part of the latter investigations (−)-hydroxy-acid (*ent*-**4a**) was converted to (−)-enone-ester (*ent*-**5**)[15] and this report describes the evaluation of (+)-enone-ester **5**, derived from (−)-camphor **2** (Scheme 1), as a potential intermediate in an enantiospecific synthetic approach to the limonoids.

In the initial stages of our synthetic approach enone-ester **5** was converted to the corresponding ketal-ester **6a**. Treatment of **6a** with LDA/THF followed by methyl bromoacetate and a catalytic amount of tetrabutylammonium iodide afforded the ketal-diester **6b** with >99% diastereoselectivity, as supported by TLC, GLC and NMR data. The stereoselectivity of the alkylation step is consistent with our previous reports that describe the stereoselective alkylation of simple derivatives of esters **4a**[15a] and **5**.[15b] Subsequent reduction of ketal-diester **6b** (DIBAL-H, THF, 0 °C; 85%), followed by methyl ether formation (NaH, THF; MeI; 90%) ketal hydrolysis (1 mol dm^{-3} HCl, acetone; 92%) provided enone **7** in which provision has been made for the later construction of the furanoid side-chain unit that is a characteristic structural feature of most limonoids. α-Alkylation[16–21] of the thermodynamic dienolate (NaH, Me_2SO, 80 °C) of **7** with 1-iodo-3-(*tert*-butyldiphenylsilyloxy)pentane **8**[22] provided enone **9** in 65% yield. The modest yield of the desired product **9** is attributed to the fact that *O*-alkylation of the dienolate derived from **7** competes with the desired α-



TBDPS = *tert*-butyldiphenylsilyl

Scheme 1 *Reagents and conditions*: i, $(CH_2OH)_2$, PPTS, reflux, 85%; ii, LDA, THF, −78 °C then $BrCH_2CO_2Me$, −78 ° → 20 °C, 93% (based on recovered starting material); iii, DIBAL-H, THF, 0 °C, 85%; iv, NaH, THF; then MeI, 90%; v, 1 mol dm^{-3} HCl, Me_2CO, 92%; vi, NaH, Me_2SO; then 1-iodo-3-(*tert*-butyldiphenylsilyloxy)pentane **8**, 65%; vii, NaH, Me_2SO, then MeI, 80%; viii, TBAF, THF, 90%; ix, CrO_3, aq. H_2SO_4, Me_2CO, 0 °C, 87%; x, *p*-TsOH, C_6H_6, reflux, 84%.

alkylation reaction. Fortunately, the starting enone **7** can be recovered through hydrolysis of the dienol ether (1 mol dm^{-3} HCl, THF) formed *via O*-alkylation. Repetition of this enone alkylation procedure using methyl iodide yielded the β,γ-unsaturated enone **10** in 80% yield. By analogy with related reactions,[23–27] the stereochemistry of the introduced methyl group was assumed to be *anti* to the angular methyl group at C-13 (triterpenoid numbering). Removal of the silyl protective group [Bu_4NF, THF, reflux; 90%] followed by Jones oxidation provided an intermediate diketone [87%] that underwent intramolecular acid-catalysed [*p*-TsOH, C_6H_6, reflux] aldol condensation to give the tricyclic dienone **11** in 84% yield. The *anti*-relationship between C-8 and C-13 methyl groups was supported by the results of a difference NOE experiment in which irradiation of the C-8 methyl proton signal did not cause enhancement of the intensity of the C-13 methyl signal, and *vice versa*.

In summary, tricyclic dienone **11**, a potential BCD-ring intermediate for limonoid synthesis, has been prepared in ten steps from enone-ester **5**, derived from (−)-camphor **2**. It is expected that further alkylation of dienone **11** with the iodide **8** followed by cyclisation (as described above) and C-4-methylation of the resulting tetracyclic dienone should provide dienone **12** (*cf.* Scheme 1), an advanced intermediate for limonoid synthesis.

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