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Synthesis of methyl (1*R*,2*S*)-α,α-dimethyl-3-oxo-2-pentylcyclopentaneacetate. A model procedure for the preparation of chiral jasmonoids and prostaglandins

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Abstract: An expeditious procedure for the enantiospecific preparation of the *trans*-2,3-disubstituted cyclopentanone moiety starting from natural 2-norbornanones is described. New reaction conditions for the reaction of sterically hindered ketones with triflic anhydride, as well as for the S–O cleavage of bridgehead triflates have been developed.

2,3-Disubstituted cyclopentanones are an important class of organic compounds widely distributed in Nature.[1] Prostaglandins,[2] dicranenones[3] and jasmonoids[4] are examples of natural products showing this standard unit. This fact has led to numerous attempts of homochiral synthesis of *trans*-2,3-disubstituted cyclopentanones in the last few years.[5]

In preliminary work we have shown that the cleavage of C_1–C_2 bond in 2-norbornanones is a convenient method for the preparation of homochiral 3-substituted cyclopentanones.[6] We report in this communication a new and easy access to homochiral *trans*-2,3-disubstituted cyclopentanones from naturally occurring 2-norbornanones, which is exemplified by the preparation of the jasmonoid methyl (1*R*,2*S*)-α,α-dimethyl-3-oxo-2-pentylcyclopentaneacetate **8** (Scheme 1).

Treatment of (+)-(1*R*)-camphor **1** with lithium *N,N*-diisopropylamide (LDA) in tetrahydrofuran (THF) at 0°C (0.5 h) gives the corresponding enolate, whose reaction with *n*-pentyl iodide (24 h) yields 56% of a mixture of the *endo*- and *exo*-alkylation products **2**, that were separated by column chromatography (silica gel, *n*-pentane).[7] Due to steric hindrance produced by the pentyl group, the thermodynamically controlled product *endo*-**2** predominates over the less stable *exo*-**2** isomer in a ratio of 95:5.[8]

We have shown that the reaction of 2-norbornanones with triflic anhydride (Tf_2O) takes place under very mild conditions (CH_2Cl_2, room temperature).[9] However, in the case of the sterically hindered *endo*-**2**, more vigorous reaction conditions were necessary. Good results were obtained by carrying out the reaction with Tf_2O and *N,N*-diisobutyl-2,4-dimethyl-3-pentylamine (DIMPA) in the absence of solvent, under reflux (1 h). A mixture of the bridgehead triflates **3**[10] and **4** (**3**/**4**=83/17), whose separation was not successful by column chromatography, was isolated as product (95%).

As we reported earlier, the reaction of bridgehead triflates with $LiAlH_4$ affords the corresponding alcohols in good yields.[11] Strikingly, under the same conditions, S–O bond cleavage of **3** and **4** was accompanied by formation of the hydrocarbon **9**[12] in a yield up to 40% depending on the solvent (Scheme 1). This by-product **9** results from the lithium catalyzed solvolysis[13] of triflates **3** and **4**, which is favoured by the alkyl group at C_7.[14] The solvolysis reaction was avoided using methyl

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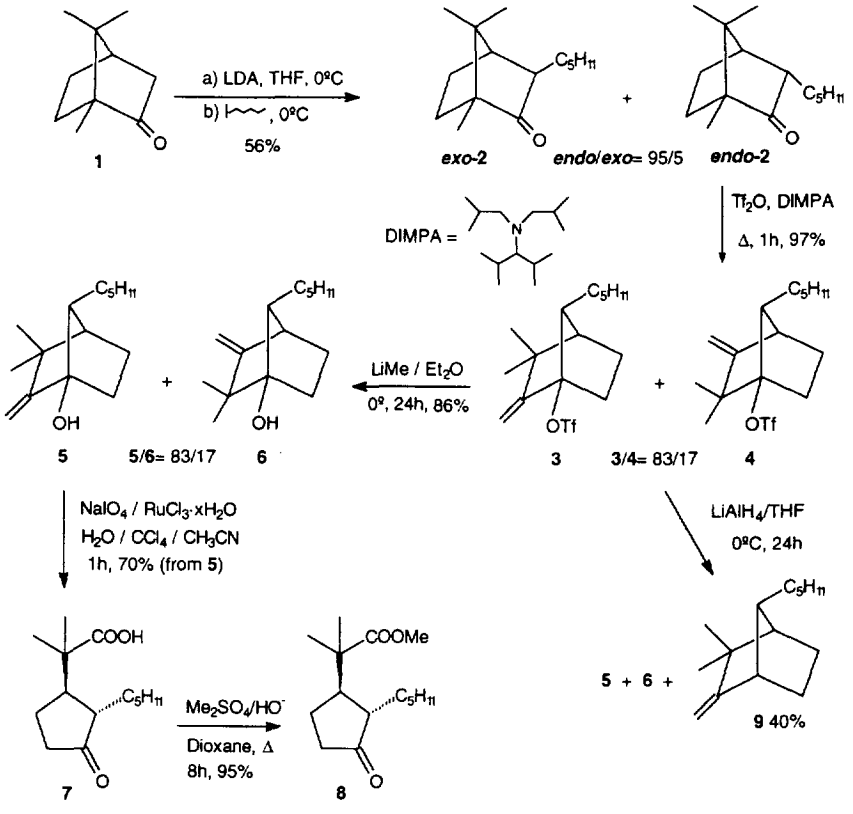

Scheme 1.

lithium as S–O cleavage reagent instead of LAH.[15] In this case, a mixture of the alcohols **5**[16] and **6** (86%, **5**/**6**=83/17), whose separation was not needed, was isolated. The formation of the jasmonoid **7**[17] is accomplished by oxidative cleavage of alcohol **5** with catalytic amounts of ruthenium trichloride along with sodium periodate as cooxidant.[18] In this process, alcohol **6** does not suffer C_1–C_2 bond cleavage, and therefore acid compound **7** can be isolated from the reaction media by extraction with 10% NaOH (70% yield from **5**). If desired, other intermediate oxidation products of **5** can be obtained following diverse reaction procedures described in the literature.[6b,19]

Finally, the reaction of **7** with methyl sulphate in basic media in refluxing dioxane gives the corresponding methyl ester **8**[20] in excellent yield (95%).

In summary, alkyl substituted naturally occurring chiral 2-norbornanones can be used for the preparation of the 2,3-disubstituted cyclopentanone moiety, as exemplified by the preparation of the ester **8**. Some modifications of the reaction procedures, described in earlier works, are necessary when the starting 2-norbornanone is highly substituted.[6]

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7. Specific rotations and NMR spectra of the synthesized products: (+)-(1*R*)-**endo-2**: $[\alpha]_D^{20}$+54,3 (c=1.05, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.40–2.30 (m, 1H), 2.10–2.00 (m,1H), 1.85–1.45 (m, 4H), 1.40–1.20 (m, 8H), 0.99 (s, 3H), 0.88 (s, 3H), 0.88 (t, 3H), 0.86 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 221.6, 58.5, 49.6, 46.0, 45.8, 31.7, 31.0, 27.6, 27.1, 22.5, 20.0, 19.5, 19.3, 14.1, 9.6. (+)-(1*R*)-**exo-2**: $[\alpha]_D^{20}$+42.5 (c=1.00, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.05–1.90 (m, 2H), 1.85–1.70 (m, 2H), 1.68–1.18 (m, 10H), 0.93 (s, 3H), 0.89 (s, 3H), 0.88 (t, 5.7 Hz, 3H), 0.83 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 222.4, 57.5, 55.5, 47.5, 46.8, 31.8, 31.7, 29.7, 29.6, 29.3, 22.6, 21.8, 20.6, 14.1, 9.5.
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10. NMR spectra (elucidated from the mixture of **3** and **4**) of the synthesized product (1*R*)-**3**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.15 (s, 1H), 4.85 (s, 1H), 2.50–2.38 (m, 1H), 2.30–2.17 (m, 1H), 1.90–1.80 (m, 2H), 1.78–1.70 (m, 1H), 1.60–1.52 (m, 1H), 1.45–1.20 (m, 8H), 1.18 (s, 3H), 1.12 (s, 3H), 0.90 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.6, 118.3 (q, 314.5 Hz, CF_3), 103.7, 101.9, 50.1, 44.5, 42.0, 31.9, 29.6, 29.3, 27.4, 26.6, 24.0, 22.6, 21.5, 14.0.
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12. NMR spectra of the synthesized product **9**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 1H), 4.46 (s, 1H), 2.43–2.38 (m, 1H), 2.03–1.92 (m, 1H), 1.80–1.60 (m, 3H), 1.54–1.40 (m, 1H), 1.36–1.14 (m, 9H), 1.05 (s, 3H), 1.03 (s, 3H), 0.89 (t, 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.0, 98.6, 50.4, 49.3, 47.9, 42.3, 32.1, 29.4, 28.3, 27.0, 26.2, 26.0, 22.6, 20.9, 14.0.
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16. NMR spectra (elucidated from the mixture of **5** and **6**) of the synthesized product (1*R*)-**5**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.61 (s, 1H), 1.83 (bs, 1H), 1.78–1.64 (m, 4H), 1.59–1.55 (m, 1H), 1.54–1.42 (m, 1H), 1.40–1.20 (m, 8H), 1.06 (s, 6H), 0.87 (t, 6.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.0, 97.1, 85.2, 51.4, 46.5, 41.0, 32.3, 30.8, 29.5, 28.1, 26.7, 24.6, 22.7, 21.9, 14.2.
17. Specific rotations and NMR spectra of the synthesized product (+)-(1*R*,2*S*)-**7**: $[\alpha]_D^{20}$+25.37 (c=0.96, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.4 (bs, 1H), 2.50–2.00 (m, 4H), 1.75–1.55 (m,

2H), 1.50–1.10 (m, 8H), 1.23 (s, 3H), 1.20 (s, 3H), 0.86 (t, 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 221.1, 184.0, 50.5, 46.8, 44.5, 37.5, 32.0, 30.1, 25.6, 23.1, 22.4, 21.5, 14.0.

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20. Specific rotations and NMR spectra of the synthesized product (+)-(1*R*,2*S*)-**8**: $[\alpha]_D^{20}$+33.3 (c=0.96, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.44–1.96 (m, 5H) 1.70–1.57 (m, 2H), 1.46–1.10 (m, 7H), 1.21 (s, 3H), 1.18 (s, 3H), 0.87 (t, 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 221.0, 177.7, 51.7, 50.5, 47.3, 44.5, 37.5, 32.1, 30.0, 25.8, 23.5, 22.5, 22.3, 21.5, 14.0.

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