



Synthesis of Homochiral 3-Substituted Cyclopentanones from 2-Norbornanones

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Abstract: The cleavage of the C₁-C₂ bond in norbornane derivatives is accomplished by base-promoted hydrolysis of α -nitroketones, periodate oxidation or Beckmann fragmentation of suitable precursors prepared from the 2-norbornanones 1. These reactions are the basis for the synthesis of the 3-substituted homochiral cyclopentanones 6, 10 or 15.

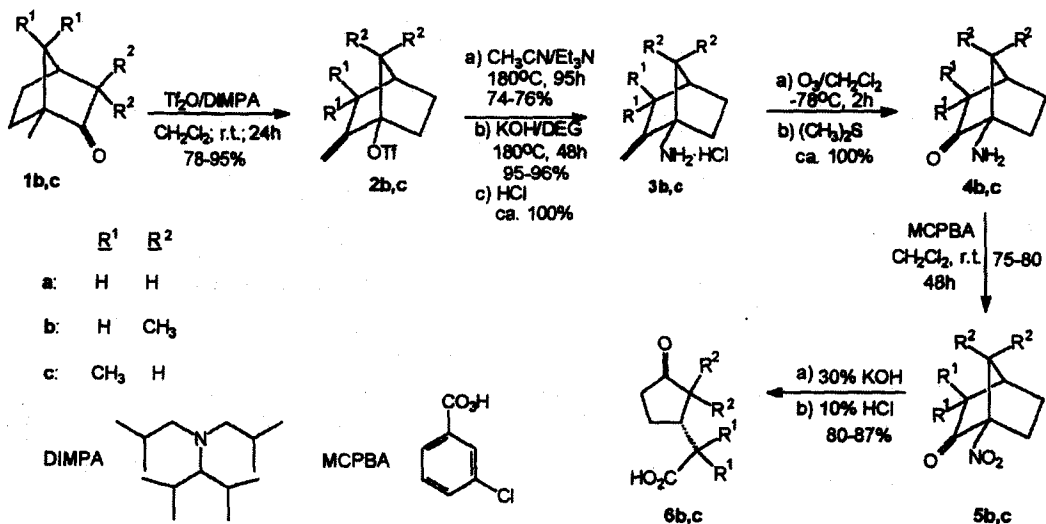
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The development of new synthetic methods for the preparation of functionalized 3-substituted homochiral cyclopentanones is an area of interest as a result of several natural products showing this standard unit.¹

The cleavage of the C₁-C₂ bond in 2-norbornanones has been accomplished by a variety of methods² and these reactions have been employed for the preparation of lactones³ and cyclopentene derivatives.^{2,4} The only reported application to the synthesis of cyclopentanones consists in the reductive cleavage of 6-oxo-norbornane-2-carboxylates.⁵

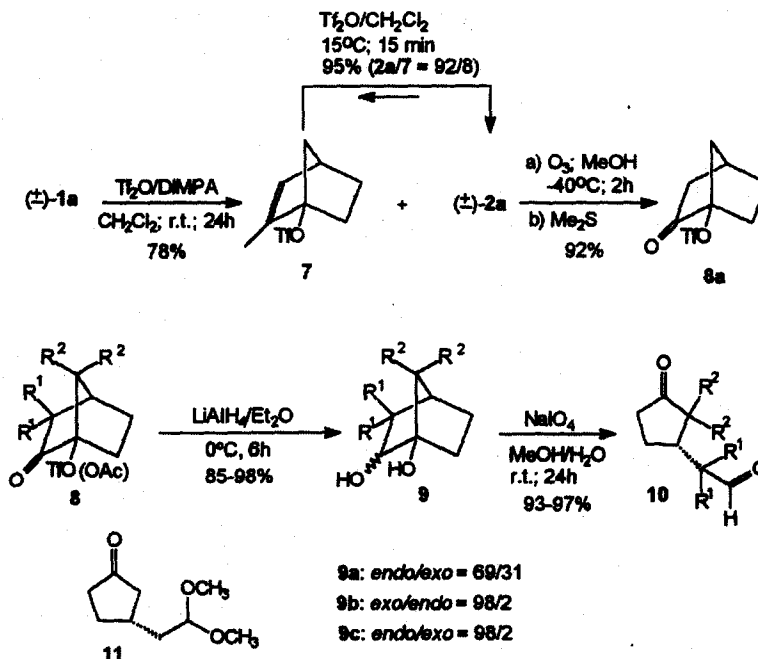
We have shown that the reaction of 2-norbornanones with triflic anhydride (Tf₂O) is a very convenient method for the preparation of substituted bridgehead derivatives.⁶ Based on this reaction, we report here on the preparation of the 3-substituted cyclopentanones 6, 10 and 15 from (\pm)-1-methyl-2-norbornanone 1a⁷ and the naturally occurring chiral ketones (-)-fenchone 1b and (+)-camphor 1c.

The preparation of the homochiral jasmonoids⁸ 6b,c is summarized in Scheme 1. The reaction of the ketones 1b,c with Tf₂O afforded the bridgehead triflates 2b,c in good yields.⁹ The corresponding bridgehead amines (hydrochloride) 3b,c were obtained by solvolysis of 2b,c in acetonitrile, a new variation of the Ritter reaction.¹⁰ The ozonolysis of 3b,c followed by oxidation with MCPBA gave the nitro ketone 5b,c,¹¹ whose basic cleavage furnished the desired keto acid 6b,c¹¹ formed by a Nef reaction of the conjugate base of the corresponding nitrocyclopentanes, which were not isolated.



Scheme 1

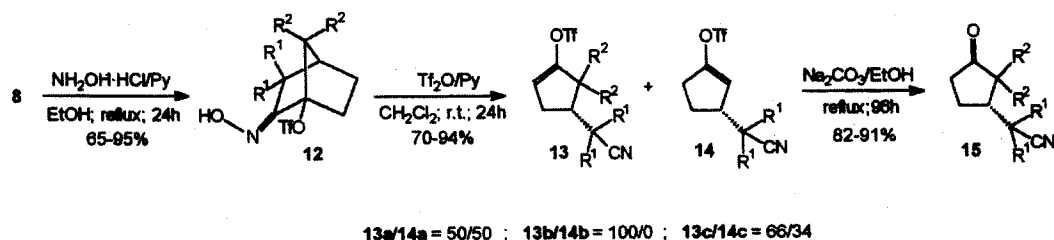
Our second method for the cleavage of the C₁-C₂ bond consists in the oxidation of 1,2-diols that were prepared from the ketotriflates **8** as shown in Scheme 2. The reaction of (±)-**1a** with Tf₂O was carried out according to our general procedure yielding a mixture of the bridgehead triflates (±)-**2a**¹² and (±)-**7**¹² (Scheme 2), which



Scheme 2

were separated by column chromatography (silica gel/*n*-pentane). The yield of (\pm)-**2a** could be improved until (\pm)-**2a**/ \pm -**7** = 92/8 by treatment with TfOH. The ozonolysis⁹ of (\pm)-**2a** afforded 2-oxo-1-norbornyl triflate (\pm)-**8a**, whose reduction with LiAlH₄ furnished a mixture of the *endo*- and *exo*-1,2-norbornanediols (\pm)-**9a**¹³ (*endo/exo* = 69/31). The diol (+)-*exo*-**9b** (*exo/endo* = 98/2) was obtained in an analogous manner from (-)-fenchone **1b**.⁹ Nevertheless, the diol (-)-*endo*-**9c** (*endo/exo* = 98/2) was obtained from camphor through the corresponding 2-oxo-1-norbornyl acetate in order to avoid ring contraction.⁹ The oxidative cleavage of the diols **9** was straightforwardly achieved by reaction with NaIO₄¹⁴ in H₂O/MeOH (50/50 v/v), affording the keto aldehydes **10**¹⁵ in good yields (Scheme 2). In the case of the oxidation of the mixture *endo/exo*-(\pm)-**9a** a small amount of the acetal (\pm)-**11**¹⁵ (14%) was formed as by-product; however, due to the higher solubility of **9a** in water, the formation of (\pm)-**11** could be avoided by employing only water as solvent (93%).

The key step of our third method for the preparation of the title compounds is based on the Beckmann fragmentation of the oximes **12** (Scheme 3), that was realized according to our method consisting in the reaction of the oximes with Tf₂O/Pyridine.¹⁶ Thus, the fragmentation of the oximes **12** yielded the vinyl triflates **13** and **14**,¹⁶ whose solvolysis in EtOH/Na₂CO₃¹⁷ afforded the cyanoketones **15**¹⁸ in good yields.



Scheme 3

In summary, we have presented convenient and easy methods for the preparation of functionalized 3-substituted cyclopentanones, which are interesting intermediates in the synthesis of biologically active compounds.¹

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- 11) Specific rotations and ^{13}C -NMR (75 MHz; CDCl_3 ; TMS) spectra of the synthesized products: (-)-(1R)-5b: δ : 203.0, 101.0, 49.8, 42.7, 42.2, 26.4, 25.8, 20.7, 18.8; $[\alpha]_{\text{D}}^{20}$ -40.1 ($c=0.80$, CH_2Cl_2); (+)-(1R)-5c: see lit¹⁹; (+)-(1S)-6b: δ : 222.3, 178.5, 47.4, 43.3, 35.9, 34.6, 25.0, 22.3, 18.0; $[\alpha]_{\text{D}}^{20}$ +43.2 ($c=0.56$, CH_2Cl_2); (+)-(1R)-6c: δ : 218.8, 182.9, 44.6, 43.5, 40.3, 38.8, 24.3, 22.4, 22.3; $[\alpha]_{\text{D}}^{20}$ +129.4 ($c=0.89$, CH_2Cl_2).
- 12) ^{13}C -NMR (75 MHz; CDCl_3 ; TMS) spectra of the synthesized products: (\pm)-2a: δ : 148.1, 118.2 (q), 103.9, 101.0, 41.1, 37.1, 33.5, 32.0, 28.0; (\pm)-7: δ : 141.9, 129.2, 118.1 (q), 104.8, 51.4, 37.5, 28.4, 28.3, 11.2.
- 13) ^{13}C -NMR (75 MHz; CDCl_3 ; TMS) spectra of the synthesized products: (\pm)-endo-9a: δ : 80.5, 75.1, 42.4, 38.8, 33.7, 30.4, 26.0; (\pm)-exo-9a: δ : 83.4, 74.0, 41.4, 38.8, 32.2, 30.6, 29.8.
- 14) (a) Hudlicky, M. *Oxidations in Organic Chemistry* American Chemical Society, Washington, 1990, pp 77-84 and 96-98. (b) General Procedure: To a stirred solution of sodium *meta*-periodate (6.0 mmol) in water (25 mL) was added dropwise a solution of 9 (4.5 mmol) in methanol (water in the case of 9a) (25 mL). The mixture was stirred at room temperature for 24 h and the reaction was monitored by GC. After completion of the reaction, the mixture was diluted with water (50 mL), extracted with ether (4x25 mL) and dried (MgSO_4). Evaporation of solvent gave the pure 3-oxocyclopentane-acetaldehyde 10. Yield: 93-97% (GC pure, column type: OV-101, 25 m).
- 15) Specific rotations and ^{13}C -NMR (75 MHz; CDCl_3 ; TMS) spectra of the synthesized products: (\pm)-10a: δ : 218.1, 200.5, 49.0, 44.2, 37.9, 30.7, 29.0; (+)-(1S)-10b: δ : 221.5, 200.9, 47.0, 44.2, 40.9, 35.8, 24.9, 22.2, 18.0; $[\alpha]_{\text{D}}^{20}$ +43.1 ($c=1.67$, MeOH); (+)-(1R)-10c: δ : 217.7, 205.2, 47.2, 42.1, 39.6, 38.8, 24.0, 19.2, 19.0; $[\alpha]_{\text{D}}^{20}$ +88.8 ($c=1.50$, MeOH); (\pm)-11: δ : 219.2, 102.9, 52.5, 44.9, 38.1, 37.9, 32.9, 29.4.
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- 17) General Procedure: A mixture of 13 (3.0 mmol), sodium carbonate (1.48 g, 14.0 mmol) and ethanol (15 mL) was refluxed for 96 h. After filtration, the solvent was removed and the residue purified by column chromatography (silica gel/ CH_2Cl_2). Yield: 82-91% (GC pure, column type: OV-101, 25 m).
- 18) Specific rotations and ^{13}C -NMR (75 MHz; CDCl_3 ; TMS) spectra of the synthesized products: (+)-(1S)-15b: δ : 220.4, 118.4, 47.4, 43.7, 35.7, 24.8, 22.7, 18.0, 17.7; $[\alpha]_{\text{D}}^{20}$ +54.6 ($c=0.64$, MeOH). (+)-(1R)-15c: δ : 216.0, 122.8, 45.7, 41.0, 38.5, 36.2, 25.8, 25.4, 24.7; cf. lit²⁰; $[\alpha]_{\text{D}}^{20}$ +108.0 ($c=0.77$, MeOH).
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