Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2177-2180, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00264-9

Synthesis of Homochiral 3-Substituted Cyclopentanones from 2-Norbornanones

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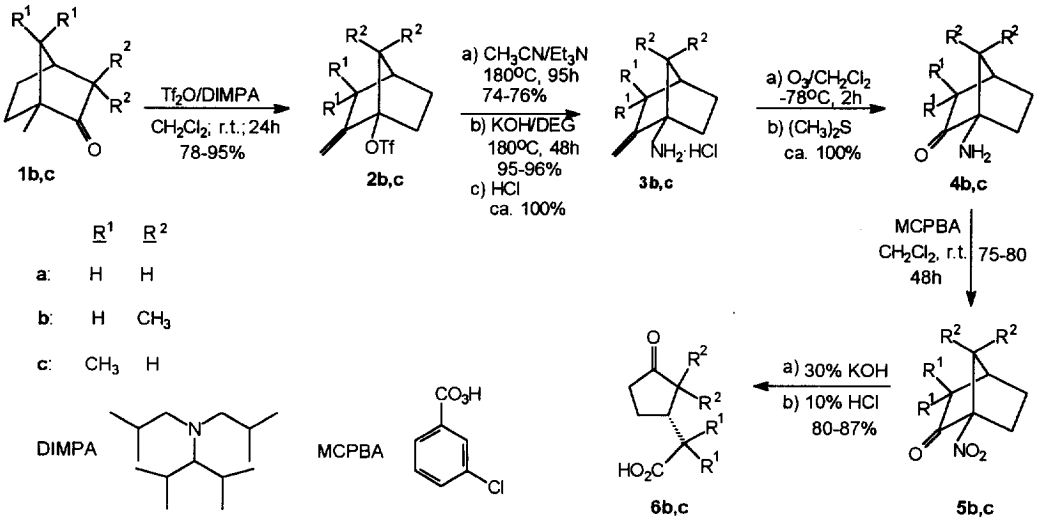
Abstract: The cleavage of the C_1-C_2 bond in norbornane derivatives is accomplished by base-promoted hydrolysis of α-nitroketones, periodate oxidation or Beckmann fragmentation of suitable precursors prepared from the 2-norbornanones **1**. These reactions are the basis for the synthesis of the 3-substituted homochiral cyclopentanones **6**, **10** or **15**.

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 C_1-C_2 bond in 2-norbornanones has been accomplished by a variety of methods[2] and these reactions have been employed for the preparation of lactones[3] 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]

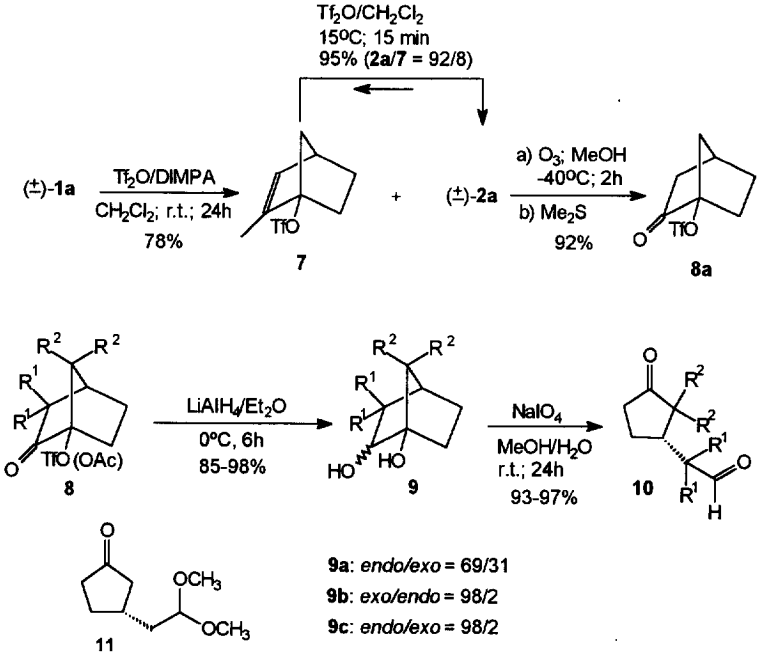
We have shown that the reaction of 2-norbornanones with triflic anhydride (Tf_2O) is a very convenient method for the preparation of substituted bridgehead derivatives.[6] Based on this reaction, we report here on the preparation of the 3-substituted cyclopentanones **6**, **10** and **15** from (±)-1-methyl-2-norbornanone **1a**[7] and the naturally occurring chiral ketones (-)-fenchone **1b** and (+)-camphor **1c**.

The preparation of the homochiral jasmonoids[8] **6b,c** is summarized in Scheme 1. The reaction of the ketones **1b,c** with Tf_2O 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,c**[11] formed by a Nef reaction of the conjugate base of the corresponding nitrocyclopentanes, which were not isolated.



Scheme 1

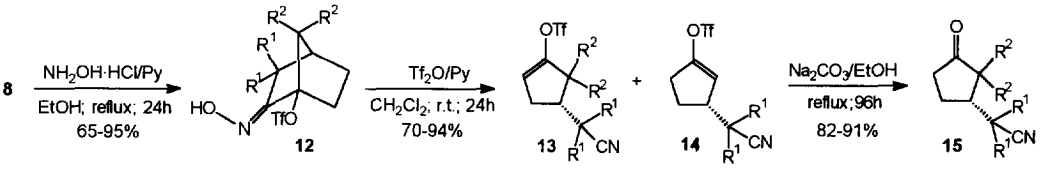
Our second method for the cleavage of the C_1-C_2 bond consists in the oxidation of 1,2-diols that were prepared from the ketotriflates **8** as shown in Scheme 2. The reaction of (±)-**1a** with Tf_2O was carried out according to our general procedure yielding a mixture of the bridgehead triflates (±)-**2a**[12] and (±)-**7**[12] (Scheme 2), which



Scheme 2

were separated by column chromatography (silica gel/*n*-pentane). The yield of (±)-**2a** could be improved until (±)-**2a**/(±)-**7** = 92/8 by treatment with TfOH. The ozonolysis[9] of (±)-**2a** afforded 2-oxo-1-norbornyl triflate (±)-**8a**, whose reduction with $LiAlH_4$ furnished a mixture of the *endo*- and *exo*-1,2-norbornanediols (±)-**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 $NaIO_4$[14] in H_2O/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*-(±)-**9a** a small amount of the acetal (±)-**11**[15] (14%) was formed as by-product; however, due to the higher solubility of **9a** in water, the formation of (±)-**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 Tf_2O/Pyridine.[16] Thus, the fragmentation of the oximes **12** yielded the vinyl-triflates **13** and **14**,[16] whose solvolysis in EtOH/Na_2CO_3[17] afforded the cyanoketones **15**[18] in good yields.



13a/14a = 50/50 ; **13b/14b** = 100/0 ; **13c/14c** = 66/34

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]

Acknowledgements: We thank the DGICYT (Spain) for financial support of this work (Grant PB 91-0354). S. de la M. C. and P. M. R. thank the Ministerio de Educación y Ciencia and Universidad Complutense, respectively, for a fellowship.

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11) Specific rotations and ^{13}C-NMR (75 MHz; $CDCl_3$; TMS) spectra of the synthesized products: (-)-(1*R*)-**5b**: δ: 203.0, 101.0, 49.8, 42.7, 42.2, 26.4, 25.8, 20.7, 18.8; $[\alpha]_D^{20}$ - 40.1 (c=0.80, CH_2Cl_2); (+)-(1*R*)-**5c**: see lit[19]; (+)-(1*S*)-**6b**: δ: 222.3, 178.5, 47.4, 43.3, 35.9, 34.6, 25.0, 22.3, 18.0; $[\alpha]_D^{20}$ + 43.2 (c=0.56, CH_2Cl_2); (+)-(1*R*)-**6c**: δ: 218.8, 182.9, 44.6, 43.5, 40.3, 38.8, 24.3, 22.4, 22.3; $[\alpha]_D^{20}$ + 129.4 (c=0.89, CH_2Cl_2).

12) ^{13}C-NMR (75 MHz; $CDCl_3$; TMS) spectra of the synthesized products: (±)-**2a**: δ: 148.1, 118.2 (q), 103.9, 101.0, 41.1, 37.1, 33.5, 32.0, 28.0; (±)-**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: (±)-*endo*-**9a**: δ: 80.5, 75.1, 42.4, 38.8, 33.7, 30.4, 26.0; (±)-*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 (25mL) 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: (±)-**10a**: δ: 218.1, 200.5, 49.0, 44.2, 37.9, 30.7, 29.0; (+)-(1*S*)-**10b**: δ: 221.5, 200.9, 47.0, 44.2, 40.9, 35.8, 24.9, 22.2, 18.0; $[\alpha]_D^{20}$ +43.1 (c=1.67, MeOH); (+)-(1*R*)-**10c**: δ: 217.7, 205.2, 47.2, 42.1, 39.6, 38.8, 24.0, 19.2, 19.0; $[\alpha]_D^{20}$ + 88.8 (c=1.50, MeOH); (±)-**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 purifiedd 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: (+)-(1*S*)-**15b**: δ: 220.4, 118.4, 47.4, 43.7, 35.7, 24.8, 22.7, 18.0, 17.7; $[\alpha]_D^{20}$ +54.6 (c=0.64, MeOH). (+)-(1*R*)-**15c**: δ: 216.0, 122.8, 45.7, 41.0, 38.5, 36.2, 25.8, 25.4, 24.7; cf. lit[20].; $[\alpha]_D^{20}$ +108.0 (c=0.77, MeOH).

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(*Received in UK* 14 *May* 1996)