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ENANTIOSPECIFIC SYNTHESIS OF 3-SUBSTITUTED ALKYLIDINECYCLOPENTANES

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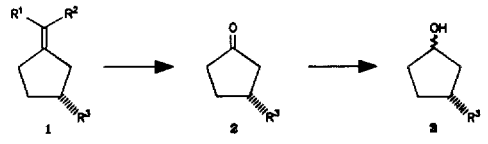
Summary: *The solvolysis of (-)-(1R)-2,2-dimethyl-3-oxotrifluoromethylsulfonyloxynorbornane [(-)-8] in 60% ethanol takes place with cleavage of C-2/C-3 bond to afford a mixture of (-)-(1R)-3-(1-methylethylidene)cyclopentane carboxylic acid (-)-(**1c**) (56%) and its corresponding ethyl ester (-)-**1d** (21%).*

Cyclopentane derivatives are an important class of organic compounds most widely distributed in nature.[1-5] This has led to numerous attempts to synthesize cyclopentane derivatives in the last few years.[6-12] 3-Substituted 1-alkylidencyclopentanes **1**[3,6-8] have been shown to be a very useful building block, which can easily lead to 3-substituted cyclopentanones **2**[9-11] and cyclopentanols **3**.[4,5] The synthesis of **1-3** is not easy and especially in the case of asymmetric synthesis the ee has amounted only to a maximum of 50%, e.g. (*3R*)-3-methylcyclopentanone (**2e**) (Scheme 1).[12]

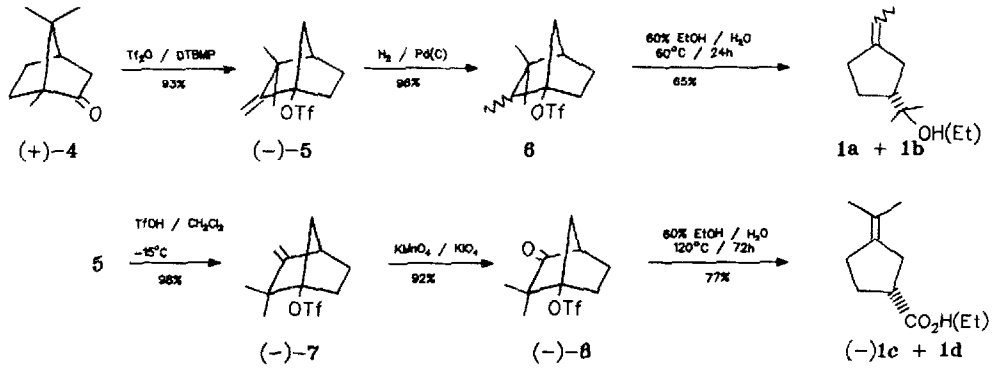
Scheme 1



1-3	a	b	c	d	e
R^1	Me(H)	Me(H)	Me	Me	–
R^2	Me(H)	Me(H)	Me	Me	–
R^3	$C(Me_2)OH$	$C(Me_2)OEt$	CO_2H	CO_2Et	Me

We have observed earlier[13] that a mixture of fragmentation products, *E/Z*-(*3R*)-1-ethylidene-3(1-hydroxy-1-methylethyl)cyclopentane (**1a**) and its ethyl ether (**1b**) results from the solvolysis of a mixture of *endo*- and *exo*-(*1S*)-2,3,3-trimethyl-1-trifluoromethylsulfonyloxynorbornane (**6**) in 60% aqueous ethanol. We report here on the enantiospecific synthesis of (-)-(*3R*)-3-(1-methylethylidene)cyclopentanecarboxylic acid [(-)-**1c**] and its corresponding ethyl ester [(-)-**1d**], which are important as chiral building blocks for the synthesis of various natural products possessing cyclopentane moiety.[3,6-11].

Scheme 2



DTBMP = 2,6-di-tert-butyl-4-methylpyridine

Treatment of (-)-(4*R*)-4-trifluoromethylsulfonyloxycamphene [(-)-**5**][14] with triflic acid in CH_2Cl_2 at -15°C effects a Nametkin rearrangement to give (-)-(1*R*)-1-trifluoromethylsulfonyloxycamphene [(-)-**7**] (Scheme 2). However, when the isomerization was carried out at room temperature,[14] racemization occurred to give the racemic triflate (±)-**7**. The racemization of the triflate (-)-**7** probably takes place through the same mechanism as the racemization of camphor with concentrated sulfuric acid.[15] The triflate (-)-**7** was oxidized with $KMnO_4/KIO_4$ to form (-)-(1*R*)-2,2-dimethyl-3-oxo-1-trifluoromethylsulfonyloxynorbornane [(-)-**8**].[16] The solvolysis of (-)-**8** in 60% aqueous EtOH buffered with Et_3N (molar-ratio of Et_3N/ (-)-**8** = 2:1) gave a mixture of (-)-**1c** and (-)-**1d** in a ratio of 64/34 (GC). Pure (-)-**1c** (58%)[17] was isolated from the reaction mixture by extraction with NaOH and acidification and pure (-)-**1d** (21%)[18] by column chromatography on silica gel (pentane/Et_2O = 95:5). The acid **1c** can be converted to the ester **1d** or vice versa, which increased the yield of the total product to more than 70%. The products were identified by IR, NMR and mass spectral data. The ^{1}H-NMR spectra of (-)-**1c** and (-)-**1d** do not show any splitting of the peaks in the presence of added chiral shift reagent Eu(facam)$_3$. The e.e. of (-)-**1c** and (-)-**1d** (70.1%) could be determined by GC on a chiral column (25 m, octenylpermethyl-ß-cyclodextrin-siloxane). The optical rotations of the products are independent of the reaction time, which vouches for the enantiometric purity.

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References and Notes

1) R.F. Newton, S.M. Roberts, *Synthesis*, **1984**, 389. 2) F.W. Comer, F. McCapa, I.H. Qureshi, A.I. Scott, *Tetrahedron*, **1967**, *23*, 4761. 3) K. Burzin, *Ger. Offen.* DE 3216085; C.A. **1984**, *100*, 51148. 4) K. Imaki, T. Okegawa, Y. Asai, *Eur. Pat. Appl.* EP 181100; C.A. **1986**, *105*, 97180. 5) M. Imaki, Y. Asai, T. Okegawa, *Eur. Pat. Appl.* EP 210772; C.A. **1986**, *106*, 175951. 6) P. Binger, P. Wedemann, *Tetrahedron Lett.*, **1983**, *24*, 5847. 7) B.M. Trost, M.T. Chan, *J. Am. Chem. Soc.*, **1983**, *105*, 2315. 8) Oppolzer, W., Ph. Schneider, *Tetrahedron Lett.*, **1984**, *25*, 3305. 9) B.H. Lipshutz, R.S. Wilhelm, J.A. Kozlowski, *J. Org. Chem.*, **1984**, *49*, 3938. 10) R.C. Gadwood, I.M. Mallick, A.J. De Winter, *J. Org. Chem.*, **1984**, *52*, 774. 11) S.M. Bertz, G. Dabbagh, *Tetrahedron*, **1989**, *45*, 425. 12) R.K. Dieter, M. Tokles, *J. Am. Chem. Soc.*, **1987**, *109*, 2040. 13) A.G. Martínez, E. Teso, A.G. Fraile, J. Osío, M. Hanack, L.R. Subramanian, *Tetrahedron Lett.*, **1989**, *30*, 1503. $[\alpha]_D^{20}$ = -22.9° (c = 1.6; CH_3OH). 14) A.G. Martínez, E. Teso, M. Gómez, C. Ruano, *Chem. Ber.*, **1985**, *118*, 1282. $[\alpha]_D^{20}$ = -35.4° (c = 3.9; CH_3OH). 15) A.M.T. Finch, W.R. Vaughan, *J. Am. Chem. Soc.*, **1969**, *91*, 1416. 16) $[\alpha]_D^{20}$ = -4.1° (c = 1.6; CH_3OH). IR (CCl_4): ν = 1760 (C=O) cm^{-1}; ^{13}C-NMR ($CDCl_3$): δ = 212.6 (C=O); 117.9 (CF_3); 99 (c-1); 51.2 (C-2); 47.7 (C-4); 37.4, 26.5, 22.0 (CH_2), 19.4, 18.7 (CH_3). 17) $[\alpha]_D^{20}$ = -2.6° (c = 2.0; CH_3OH). IR (CCl_4): ν = 1700 (C=O) cm^{-1}; ^{13}C-NMR ($CDCl_3$): δ = 182.4 (C=O); 132.7, 122.5 (C=C); 44.4 (C-1); 33.9, 30.2, 29.8 (CH_2); 21.0 (CH_3). 18) $[\alpha]_D^{20}$ = -3.0° (c = 1.3; CH_3OH). IR (CCl_4): ν = 1745 (C=O) cm^{-1}; ^{13}C-NMR ($CDCl_3$): δ = 175.7 (C=O); 133.0, 122.1 (C=C); 60.2 (OCH_3); 44.6 (C-1); 34.0, 29.9 (CH_2); 21.0, 20.9 (CH_3); 14.2 (CH_2-CH_3).

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