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Synthesis of Homochiral Cyclopentane Derivatives by Beckmann Fragmentation of 1-Substituted 2-Norbornanones

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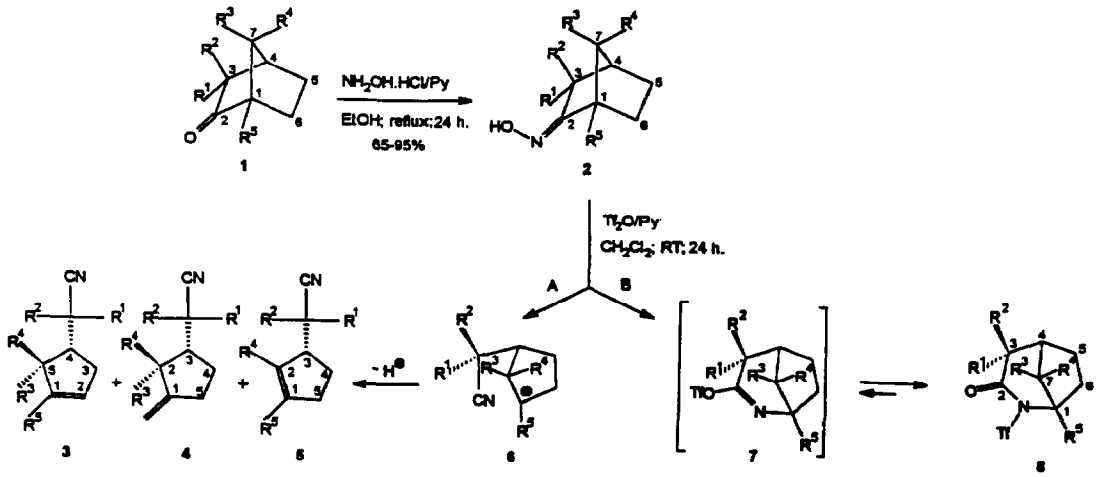
Abstract: *The fragmentation of 2-norbornanone oximes 2 was achieved by reaction with Tf_2O/pyridine under mild reaction conditions, yielding homochiral (or racemic) cyclopentane derivatives.*

Cyclopentane derivatives are a very interesting and important class of organic compounds[1] and occur widely in natural products. The enantiospecific synthesis of some homochiral cyclopentane derivatives has been carried out by Beckmann fragmentation[2] of fenchone oxime (**2j**)[3] and camphor oxime (**2i**) derivatives.[4] However, in the case of the 2-norbornane oxime (**2a**)[5] or when a relatively unstable carbocation **6** can result, the fragmentation reaction is not straightforward and a complicated mixture of fragmented and rearranged products is formed.[2]

In the present work we have investigated the utilization of triflic anhydride (Tf_2O) as reagent for the Beckmann fragmentation of the oximes **2** of 2-norbornanones **1** bringing substituents of very different stereoelectronic effects at the bridgehead position.[6]

The reaction of *anti*-oximes[7] **2a-d**, **2g** and **2i** with Tf_2O/pyridine affords only products resulting from the bridgehead cleavage **3-5**[8] in good yields (Table 1). With shorter reaction times or at lower temperature the formation of the N-triflyllactams **8** can be observed (two examples are show in Table 1). Thus, N-triflyllactams **8** resulting from a Chapman rearrangement[2a] of the not isolated imidate **7**, are the kinetically favoured reaction products. This reaction path B (Scheme 1) is the usual one by which th. Beckmann rearrangement takes place[2]. However, in contrast to the standard reagents, Tf_2O/pyridine can attack the N-triflyllactams **8** at higher temperatures (or larger reaction times) with reversion of the Chapman rearrangement. The termodynamically favoured products **3-5** are then formed by fragmentation of the unstable imidates **7** *via* the cations **6** (Scheme 1).

Scheme 1



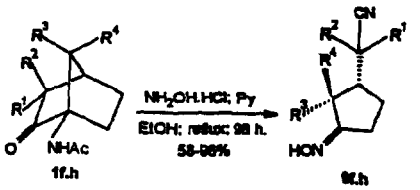
1-8	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	H	H	H	H	OTf
c	CH_3	CH_3	H	H	OTf
d	CH_3	CH_3	H	H	I
e	CH_3	CH_3	H	H	CN
f	CH_3	CH_3	H	H	NHAc
g	H	H	CH_3	CH_3	OTf
h	H	H	CH_3	CH_3	NHAc
i	H	H	CH_3	CH_3	CH_3
j	CH_3	CH_3	H	H	CH_3

Table 1: Products obtained by reaction of oximes **2** with Tf_2O/Py in CH_2Cl_2; 24h; RT.

2	Yield (%)	Products (%)[a]
a	29	3a(28) + 5a(14) + 8a(58)
a[b]	29	3a(59) + 5a(21) + 8a(20)
b	94	3b(50) + 5b(50)
c	77	3c(66) + 5c(34)
d	90	3d(48) + 5d(27) + 8d(25)
d[b]	76	3d(63) + 5d(37)
e	49	11(72) + 12(28)
g	70	3g(100)
i	82	3i(71) + 4i(29)

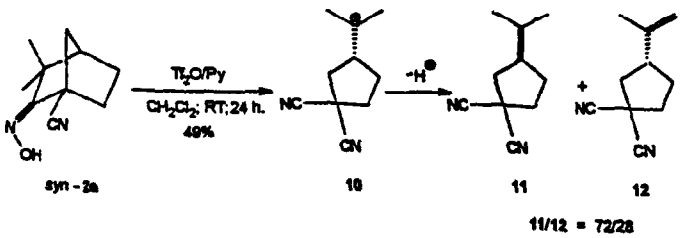
[a]Determinated by GLC (OV-101, 25m). [b]Tf_2O/Py in $CHCl_3$; 24h; 75°C.

The fragmentation of the oximes **2f** and **2h** is so fast (probably through the stable cations **6f,h**; reaction type A) that the fragmented oximes *syn/anti*-**9f** (50/50) and (+)-*anti*-**9h** are formed during the oximation of the ketones (-)-**1f** and (-)-**1h** (Scheme 2).



Scheme 2

The reaction of a mixture of *syn*/*anti*-**2e** (83/17) with Tf_2O/pyridine under our standard conditions (Table 1) yield only products (**11**+**12**) formed by fragmentation of the C_2-C_3 bond, which is *anti* to the OH group in *syn*-**2e**. Due to the -I effect of CN group, the fragmentation of *anti*-**2e** is slower than its Lewis-acid (Tf_2O) catalyzed isomerization to *syn*-**2e**.[2]



Scheme 3

In conclusion, our method is the best procedure for the fragmentation of 2-norbornane oximes **2**, because the Beckmann rearrangement can be avoided even in the present of -I substituents. Moreover, the reaction conditions are very mild. Further work on the preparation of valuable jasmonic acid derivatives [1,8] from cyclopentenyl triflates **3b,c,g** and **5b,c,g** are in progress.

Experimental

^1H NMR and ^{13}C NMR were recorded on Bruker-AC 250 MHz spectrometer in deuterochloroform and chemical shifts are expresed in ppm. IR spectra were recorded on Perkin-Elmer 781 spectrometer. Mass spectra were recorded on Varian-MAT 711 instrument (**11** and **12** were analized by GLC-MS). Optical rotations were measured on Perkin-Elmer 241 polarimeter. Melting points were determined on Gallemkamp apparatus and are uncorrected. Capillary GLC data were recorded on Perkin-Elmer Sigma 300.

General procedure for the synthesis of oximes 2 and 9

A solution of ketone **1** (5.0 mmol), pyridine (15.0 mmol) and $NH_2OH.HCl$ (25 mmol) in 96% ethanol (25 ml) was refluxed 24 h (96 h for oximes **9**) and the reaction was monitored by GLC. The ethanol was evaporated under reduced pressure and 10% HCl (50 ml) was added over the residue. The mixture was extracted with Et_2O (4x25 ml),

washed with brine (2x25 ml) and dried over $MgSO_4$. The extract was concentred under reduced pressure and the oximes were purified by recrystalization from ethanol.

(±)-*anti*-1-trifluoromethylsulfonyloxy-2-norbornanoxime (2b)

^{1}H NMR δ: 8.81 (1H bs), 2.58-1.95 (8H, m), 1.55-1.50 (1H, m); ^{13}C NMR δ: 159.0 (C2), 118.0 (CF_3, q), 96.4 (C1), 41.7, 34.2, 31.2, 31.0, 27.6; IR (CCl_4) ν: 3580 (OH), 3320 (OH), 2990, 1425 (OTf), 1255, 1200 (OTf), 1150 (OTf), 1070, 1000, 940, 870 cm^{-1}; mp: 83.9-85.2°C.

(-)-(1*R*)-*anti*-3,3-dimethyl-1-trifluoromethylsulfonyloxy-2-norbornanoxime (2c)

^{1}H NMR δ: 8.49 (1H, bs), 2.45 (1H,m), 2.20 (1H, m), 2.10-1.80 (5H, m), 1.38 (3H, s), 1.36 (3H, s); ^{13}C NMR δ: 163.1 (C2), 118.2 (CF_3, q), 96.2 (C1), 43.8, 43.7, 39.1, 31.3, 23.7, 22.7, 22.0; IR (CCl_4) ν: 3580 (OH), 3300 (OH), 2960, 1420 (OTf), 1250, 1220 (OTf), 1150 (OTf), 1060, 1030, 990, 900 cm^{-1}; MS m/e (%B): 301 ($M^{+\cdot}$, 98), 286 (7), 284 (18), 259(9), 258 (45), 256 (12), 232 (3), 168 (99), 152 (11), 151 (58), 126 (100), 69 (99); mp: 109.6-111.5°C; $[\alpha]_D^{20}$ -32.2 (c=1.10, MeOH).

(-)-(1*R*)-*anti*-3,3-dimethyl-1-iodo-2-norbornanoxime (2d)

^{1}H NMR δ: 8.63 (1H, bs), 2.36-2.18 (2H, m), 2.10-1.90 (2H, m), 1.88-1.76 (2H, m), 1.67 (1H, m), 1.35 (3H, s), 1.33 (3H, s); ^{13}C NMR δ: 167.2 (C2), 48.5, 48.4, 42.9, 41.1, 37.4, 26.4, 22.7, 21.8; IR (KBr) ν: 3090 (OH), 2990, 1470, 1200, 960, 800 cm^{-1}; mp: 193.5-195.9°C; $[\alpha]_D^{20}$ -87.1 (c=0.85, MeOH). The structure was also analyzed by X-Ray crystallography.[7]

(1*R*)-*syn*-1-cyano-3,3-dimethyl-2-norbornanoxime (*syn*-2e) and (1*R*)-*anti*-1-cyano-3,3-dimethyl-2-norbornanoxime (*anti*-2e)

^{1}H NMR δ: 9.34 (*syn*-OH, bs), 8.79 (*anti*-OH), 2.27-1.54 (m), 1.27 (*anti*-Me, s), 1.26 (*anti*-Me, s), 1.15 (*syn*-Me, s), 1.10 (*syn*-Me, s); *syn*-^{13}C NMR δ: 163.4 (C2), 119.9 (CN), 46.9, 43.6, 42.4, 39.9, 32.3, 26.2, 23.7, 23.4; *anti*-^{13}C NMR δ: 164.9 (C2), 118.8 (CN), 48.6, 46.9, 43.1, 41,3, 32.6, 23.5, 22.5, 21.3; IR ($CHCl_3$) ν: 3580 (OH), 3260 (OH), 2980, 2250 (CN), 1470, 1390, 1370, 960 cm^{-1}.

(+)-(1*R*)-*anti*-7,7-dimethyl-1-trifluoromethylsulfonyloxy-2-norbornanoxime (2g)

^{1}H NMR δ: 7.70 (1H, bs), 2.90 (1H, m), 2.45-2.05 (4H, m), 1.82 (1H, t), 1.52 (1H, m), 1.17 (3H, m), 1.09 (3H, s); ^{13}C NMR δ: 159.5 (C2), 118.2 (CF_3, q), 99.2 (C1), 49.3, 38.2, 32.4, 27.2, 27.1, 18.4, 17.6; IR (KBr) ν: 3400 (OH), 3000, 1410 (OTf), 1250, 1200 (OTf), 1150 (OTf), 1080, 1010, 985, 940, 875, 850 cm^{-1}; mp: 179.5-181.6°C; $[\alpha]_D^{20}$ +40.7 (c=1.44, MeOH).

(3*R*)-*syn*-3-(1-cyano-1-methylethyl)cyclopentanoxime (*syn*-9f) and (3*R*)-*anti*-3-(1-cyano-1-methylethyl)cyclopentanoxime (*anti*-9f)

^{1}H NMR δ: 8.88 (bs), 2.84-2.64 (m), 2.40-2.16 (m), 2.06-1.82 (m), 1.68-1.50 (m), 1.34-1.28 (3 s); *syn*-^{13}C NMR δ: 164.0 (C1), 123.2 (CN), 47.3, 36.0, 30.0, 27.3, 26.7, 25.5, 25.5; *anti*-^{13}C NMR δ: 164.4 (C1), 123.2 (C2), 47.5, 35.9, 33.3, 30.1, 26.7, 25.9, 25.7; IR (KBr) ν: 3260 (OH), 2990, 2230 (CN), 1690, 1420, 1390, 1370, 1270, 1220, 940 cm^{-1}; MS m/e (%B): 166 ($M^{+\cdot}$, 76), 165 (6), 151 (12), 149 (6), 148 (4), 139 (6), 138 (6), 124 (15), 123 (6), 122 (12), 109 (50), 98 (100), 80 (50).

(+)-(3*S*)-*anti*-3-cyanomethyl-2,2-dimethylcyclopentanoxime (9h)

^{1}H NMR δ: 8.48 (1H, bs), 2.69 (1H, m), 2.46 (1H, m), 2.28-1.98 (4H, m), 1.58 (1H, m), 1.22 (3H, s), 0.98 (3H, s); ^{13}C NMR δ: 170.3 (C1), 118.6 (CN), 45.5, 43.7, 26.5, 24.8, 24.8, 20.8, 17.2; IR (KBr) ν: 3270 (OH), 2970,

2250 (CN), 1710, 1460, 1420, 1390, 1370, 950, 760 cm^{-1}; $[\alpha]_D^{20}$ +14.6 (c=3.10, MeOH).

General procedure for the reaction of oximes 2 with Tf_2O/Py

To a 0°C cooled solution of oxime (5.0 mmol) and pyridine (7.0 mmol) in CH_2Cl_2 (10 mL), was added a solution of Tf_2O (6.0 mmol) in CH_2Cl_2 (5 mL). After 24 h at room temperature (the reaction was monitored by GLC), the reaction mixture was treated with saturated solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (5x10 mL). The organic layer was washed with 10% HCl (2x25 mL), saturated solution of $NaHCO_3$ (25 mL), brine (2x25 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure and the products were purified by elution chromatography (silicagel, CH_2Cl_2).

For **3a**, **3i**, **4i** and **5a** see literature.[2]

(±)-4-cyanomethyl-1-trifluoromethylsulfonyloxycyclopentene (3b) and (±)-3-cyanomethyl-1-trifluoromethylsulfonyloxycyclopentene (5b).

^1H NMR δ: 5.58-5.56 (m), 3.16-3.02 (m), 2.88-2.50 (m), 2.42 (d), 2.40 (d), 2.38-2.10 (m), 1.80-1.68 (m); **3b**-^{13}C NMR δ: 146.9 (C1), 118.3 (CF_3, q), 117.9 (CN), 116.4 (C2), 33.7, 31.8, 30.5, 23.5; **5b**-^{13}C NMR δ: 151.3 (C1), 118.3 (CF_3, q), 117.8 (C2), 117.6 (CN), 38.0, 36.4, 26.8, 23.1; IR (CCl_4) ν: 2990, 2245 (CN), 1660 (C=C), 1430 (OTf), 1250, 1220 (OTf), 1150 (OTf), 1130, 910 cm^{-1}.

(4*R*)-4-(1-cyano-1-methylethyl)-1-trifluorometahylsulfonyloxycyclopentene (3c) and (4*R*)-3-(1-cyano-1-methylthyl)-1-trifluoromethylsulfonyloxycyclopentene (5c)

^1H NMR δ: 5.75-5.65 (m), 3.20-2.94 (m), 2.84-2.24 (m), 2.10-1.96 (m), 1.43 (s), 1.42 (s), 1.41 (s); **3c**-^{13}C NMR δ: 147.0 (C1), 122.9 (CN), 118.3 (CF_3, q), 116.7 (C2), 44.5, 36.1, 30.9, 24.8, 24.4; **5c**-^{13}C NMR δ: 151.8 (C1), 123.5 (CN), 118.3 (CF_3, q), 116.0 (C2), 50.1, 36.1, 30.7, 24.0, 23.9, 23.6; IR (CCl_4) ν: 2990, 2240 (CN), 1660 (C=C), 1430 (OTf), 1280 (OTf), 1220 (OTf), 1150, 1130, 900 cm^{-1}.

(4*R*)-4-(1-cyano-1-methylethyl)-1-iodocyclopentene (3d) and (4*R*)-3-(1-cyano-1-methylethyl)-1-iodocyclopentene (5d)

^1H NMR δ: 6.10-6.05 (m), 2.85-1.75 (m), 1.32 (s), 1.29 (s); **3d**-^{13}C NMR δ: 138.5 (C2), 123.2 (CN), 90.3 (C1), 47.4, 45.8, 36.6, 35.7, 25.0, 24.9,; **5d**-^{13}C NMR δ: 137.9 (C2), 123.8 (CN), 97.1 (C1), 55.5, 43.4, 35.3, 26.8, 24.1, 24.0; IR (CCl_4) ν: 3070 (=CH), 2980, 2240 (CN), 1610 (C=C), 1470, 1460, 1395, 1375 cm^{-1}. Rotations were not measured.

(+)-(4*S*)-4-cyanomethyl-5,5-dimethyl-1-trifluoromethylsulfonyloxycyclopentene (3g)

^1H NMR δ: 5.58 (1H, s), 2.67 (1H, m), 2.55-2.30 (3H, m), 1.22 (3H, s); ^{13}C NMR δ: 154.0 (C1), 118.2 (CF_3, q), 118.1 (CN), 111.1 (C2), 44.6, 43.1, 31.6, 24.5, 18.8, 17.4; IR (CCl_4) ν: 2980, 2250 (CN), 1650 (C=C), 1425 (OTf), 1220 (OTf), 1145 (OTf), 1090, 1070, 875 cm^{-1}; $[\alpha]_D^{20}$ +7.2 (c=0.76, CH_2Cl_2).

(±)-2-trifluoromethylsulfonyl-2-azabicyclo[3.2.1]octan-3-one (8a)

^1H NMR δ: 4.78 (1H, m), 2.76 (1H, ddd), 2.60 (1H, m), 2.50 (1H, dt), 2.10-1.60 (6H, m); ^{13}C NMR δ: 169.7 (C2), 119.0 (CF_3, q), 61.2 (C1), 43.5, 36.6, 33.3, 32.3, 28.8; IR (CCl_4) ν: 2960, 1745 (CO), 1415 (NTf), 1380, 1220 (NTf), 1140 (NTf), 1090, 1070, 1060, 910 cm^{-1}; MS m/e (%B): 257 ($M^{+\cdot}$, 3), 124 (6), 110 (75), 95 (18), 82 (21), 80 (22), 69 (83), 68 (100).

(-)-(1*R*)-4,4-dimethyl-1-iodo-2-trifluoromethylsulfonyl-2-azabicyclo[3.2.1]octan-3-one (8d)

^1H NMR δ: 3.07 (1H, m), 2.69 (1H, dd), 2.52 (1H, d), 2.41 (1H, m), 2.13-1.77 (3H, m), 1.33 (3H, s), 1.18 (3H,

s); ^{13}C NMR δ: 176.9 (C2), 119.2 (CF_3, q), 52.5, 48.7, 48.7, 44.8, 42.5, 26.9, 24.6, 24.3; IR (CCl_4) ν: 2980, 1750 (CO), 1410 (NTf), 1220 (NTf), 1130 (NTf), 1080, 1040 cm^{-1}; MS m/e (%B). 411 ($M^{+\cdot}$, 1), 378 (1), 314 (4), 284 (26), 256 (100), 242 (13), 214 (76), 193 (41), 123 (11), 122 (11), 108 (12), 107 (40); $[\alpha]_D^{20}$ -136.0 (c=0.52. MeOH).

3-isopropylidencyclopentan-1,1-dicarbonitrile (11) and (3*R*)-3-(2-propenyl)cyclopentan -1,1-dicarbonitrile (12) ^1H NMR δ: 4.78 (s), 4.74 (s), 2.94 (s), 2.82-1.70 (m), 1.69 (s), 1.60 (s); **11**-^{13}C NMR δ: 128.2 (C3), 125.7 (C6), 116.1 (CN), 116.1 (CN), 42.4, 38.0, 33.9, 27.8, 21.2, 21.2; **12**-^{13}C NMR δ: 143.6 (C6), 116.8 (CN), 116.6 (CN), 111.3 (C7), 45.4, 43.1, 38.6, 32.9, 29.4, 20.7; IR (CCl_4) ν: 3080 (=CH), 2980, 2250 (CN), 1650 (C=C), 1445, 1380, 905 cm^{-1}; **11**-MS m/e (%B): 160 ($M^{+\cdot}$, 32), 145 (19), 133 (12), 118 (47), 104 (7), 94 (21), 91 (19), 82 (23), 79 (32), 67 (100), 59 (66), 43 (39), 42 (63), 41 (73); **12**-MS m/e (%B): 160 ($M^{+\cdot}$, 15), 145 (10), 132 (11), 118 (39), 105 (15), 94 (31), 82 (22), 79 (20), 67 (100), 53 (19), 41 (17).

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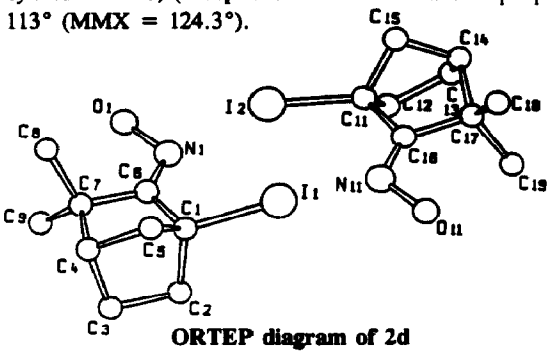
6) The ketones (±)-**1a** and (+)-**1i** are commercially availables (FLUKA). (±)-**1b**, (-)-**1c** and (+)-**1g** were obtained according to: Martínez, A.G.; Teso, E.; Osío, J.; Rodríguez, M.E.; de la Moya, S.; Hanack, M.; Subramanian, L.R. *Tetrahedron Asymm.* **1993**, *4*, 2333. The ketones (-)-**1d**, (+)-**1e**, (-)-**1f** and (-)-**1h** were prepared by ozonolysis of the corresponding methylidene derivatives (result not published).

7) The *anti* configuration of the oximes **2** and **9** were determinated by comparation of the ^1H- and ^{13}C-NMR espectra with the described in the literature for *anti*-**2a** and *anti*-**2i**[2,4] (s. Experimental). High quality crystals were obtained only from (-)-*anti*-**2d**. The X-ray structure agrees with the calculated by MMX (PCMODEL, Serena Software): E (Kcal/mol): *anti*-**2d** = 31.4, *syn*-**2d** = 32.8; (exceptions are: bond distance O_1-N_1 = 1.43 Å (MMX = 1.310 Å), and bond angle O_1-N_1-C_6 = 113° (MMX = 124.3°).



ORTEP diagram of 2d

In the case of the ketone (+)-**1e**, a mixture of the oximes *anti*- (17%) and *syn*-**2e** (83%) was formed. The reason for the *syn*-**2e** high ratio is unknown. MMX predicts a little more of stability for the *anti*- (30.0 Kcal/mol) against the *syn*-oxime (30.4).

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