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Resolution of 7-oxabicyclo[2.2.1]hept-5-en-2-one via cyclic aminals

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Abstract

High yielding resolution of racemic 7-oxabicyclo[2.2.1]hept-5-en-2-one (±)-**1** ('7-oxanorbornenone') via aminal formation with (*R*,*R*)-1,2-diphenylethylenediamine **2** is reported. Acidic hydrolysis furnishes the enantiomeric ketones (+)-**1** and (−)-**1** (≥95% ee). The chiral diamine is efficiently recovered. © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The bicyclic enones [(+)-**1** and (−)-**1**, (+)- and (−)-7-oxabicyclo[2.2.1]hept-5-en-2-one: "naked sugars of the first generation"] and their derivatives are useful chiral building blocks for the synthesis of natural products and analogs.[1–4] Several methods for their preparation in enantiomerically pure form have been reported. Strategies involving asymmetric Diels–Alder reactions controlled by chiral auxiliaries[5] and chiral Lewis acids[6] have been developed. However, all of these methods suffer either from low diastereoselectivity or tedious reaction sequences to obtain the desired ketone. For preparative purposes, the resolution of the readily available racemic 7-oxabicyclo[2.2.1]hept-5-en-2-one[1b] is still the most efficient approach. Resolution via a cyanohydrine–brucine complex[1c,7] or via sulfoximide adducts of derivatives of (±)-**1**[1c,8] have been described but the global yields are moderate. We report here an alternative resolution procedure based on formation of aminals derived from (*R*,*R*)-1,2-diphenylethylenediamine **2**.

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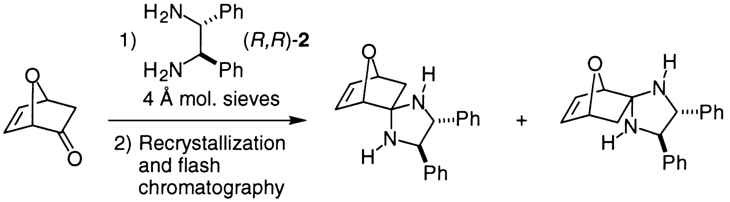
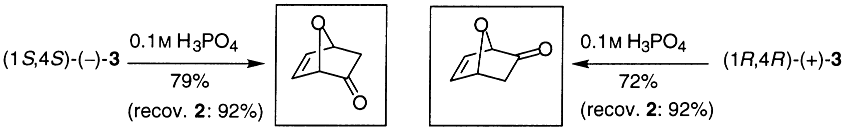
2. Results and discussion

Recently, it was reported that (*R*,*R*)-1,2-diphenylethylenediamine **2** is an efficient reagent to determine the enantiomeric purity of the substituted cycloalkanones.[9] However, to our knowledge, resolution of chiral ketones via the corresponding aminals has not yet been reported. (*R*,*R*)-1,2-Diphenylethylenediamine **2** is commercially available and can easily be prepared in enantiomerically pure form.[10] The diastereomeric aminals (1*S*,4*S*)-(−)-**3** and (1*R*,4*R*)-(+)-**3** were formed in nearly quantitative yields by the reaction of racemic 7-oxabicyclo[2.2.1]hept-5-en-2-one (±)-**1** with (*R*,*R*)-1,2-diphenylethylenediamine **2** in CH_2Cl_2 containing 4 Å molecular sieves. Running the reaction in an NMR tube showed that no kinetic resolution takes place and that conversion to the aminals is complete after 36 h. The aminals were not stable in solution unless 2% triethylamine was added to the solvent. Under these conditions, it was possible to separate the two diastereoisomers by flash chromatography on a small scale involving less than 2 g of aminals. On a larger scale, the mixture of aminals was first recrystallized from CH_2Cl_2:hexane:Et_3N to isolate (1*S*,4*S*)-(−)-**3** in 46% yield. The mother liquor mainly contained (1*R*,4*R*)-(+)-**3**, and traces of (1*S*,4*S*)-(−)-**3** were removed by flash chromatography.



(±)-**1** (1*S*,4*S*)-(−)-**3** (46%) (1*R*,4*R*)-(+)-**3** (43%)

The diastereomerically pure aminals were hydrolyzed by treatment with 0.1 M phosphoric acid and the organic phase was continuously extracted with Et_2O. This procedure displaced the equilibrium of the hydrolysis in favor of the water soluble ketones (+)-**1** and (−)-**1**. Enantiomerically enriched (+)-**1** and (−)-**1** were obtained by bulb-to-bulb distillation of the crude products. The enantiomeric excesses of both (+)-**1** and (−)-**1** were determined by gas chromatography on a chiral column (β-cyclodextrin, 65% acetoxy, 100°C) and found to be better than 99% for (1*S*,4*S*)-(−)-**1** and over 95% for (1*R*,4*R*)-(+)-**1**. After neutralization of the aqueous phase with 1 M NaOH and extraction with CH_2Cl_2, the (*R*,*R*)-1,2-diphenylethylenediamine **2** was recovered in 92% yield.



(1*S*,4*S*)-(−)-**1** (1*R*,4*R*)-(+)-**1**

A first attempt to scale up the procedure to 15 g of racemic 7-oxabicyclo[2.2.1]hept-5-en-2-one was carried out. Enantiomerically pure (≥99% ee) (1*S*,4*S*)-(−)-**1** and (1*R*,4*R*)-(+)-**1** were obtained in 33% (5.0 g) and 30% (4.4 g) yields, respectively.

3. Conclusions

This approach compares favorably with all reported resolution procedures. Moreover, the use of (*R*,*R*)- and (*S*,*S*)-1,2-diphenylethylenediamine should find broad application for the resolution of chiral ketones. Preliminary experiments with bicyclo[2.2.1]hept-5-en-2-one (norbornenone) confirms the generality of this approach.

4. Experimental

4.1. General

CH_2Cl_2 was distilled from CaH_2. For flash column chromatography (FC) and filtration, Baker silica gel (0.63–0.200 mm) was used. TLC was performed on Merck silica gel 60 F_{254} analytical plates; detection either with UV, iodine or spraying with a solution of 25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 ml conc. H_2SO_4 and 940 ml water and subsequent heating. M.p.: not corrected; Büchi Tottoli apparatus. IR: Mattson Unicam 5000; in cm^{-1}. NMR: Varian Gemini 200 (^1H 200 MHz and ^{13}C 50.3 MHz), Bruker AM 360 (^1H 360 MHz), Bruker Avance DRX-500 (^1H 500 MHz, ^{13}C 125.76 MHz); for ^1H δ in ppm relative to $CDCl_3$ (=7.26 ppm), for ^{13}C multiplicities were determined by APT sequence; coupling constants *J* are given in hertz. MS: Vacuum Generators Micromass VG 70/70E DS 11-250; EI (70 eV), CI (CH_4 gas); m/z (%). Gas chromatography: CE instruments HRGC Megaseries. Elemental analyses: Ilse Beetz, Microanalytisches Laboratorium, D-96301 Kronach, Germany and Ciba Geigy Mikrolabor, CH-1726 Marly, Switzerland.

4.2. *(1*R*,4*R*,4′*R*,5′*R*)- and (1*S*,4*S*,4′*R*,5′*R*)-4′,5′-Diphenylspiro[7-oxabicyclo[2.2.1]hept-5-en-2,2′-imidazolidine] (1*R*,4*R*)-(+)-**3** and (1*S*,4*S*)-(−)-**3***

(*R*,*R*)-Diphenylethylenediamine (**2**; 1.93 g, 9.1 mmol) was added under N_2 to a solution of (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one[1b] ((±)-**1**; 1.00 g, 9.1 mmol) in dry CH_2Cl_2 (30 ml) containing 4 Å molecular sieves (2 g). The reaction mixture was stirred for 2 days, Et_3N (1.5 ml) added and the molecular sieves then eliminated by filtration. The filtrate was concentrated. Fractional crystallization of the residue (CH_2Cl_2:hexane containing 5% Et_3N) afforded (1*S*,4*S*)-(−)-**3** (1.27 g, 46%). The mother liquor was concentrated and FC (CH_2Cl_2:hexane 1:8, 5% Et_3N) afforded the second diastereomer (1*R*,4*R*)-(+)-**3** (1.18 g, 43%). Data for (1*S*,4*S*)-(−)-**3**: m.p. 140°C (dec.). $[\alpha]^{23}_{589}$=−3.8 (c=0.29, $CHCl_3$). ^1H-NMR (360 MHz, $CDCl_3$): 7.35–7.10 (*m*, 10 arom. H), 6.68 (*dd*, *J*=5.8, 1.6, H–C(5)), 6.56 (*dd*, *J*=5.8, 1.8, H–C(6)), 5.01 (*d* (br.), *J*=4.3, H–C(4)), 4.64 (*dd*, *J*=1.8, 0.9, H–C(1)), 4.25, 4.11 (2*d*, *J*=8.7, H–C(4′), H–C(5′)), 2.45 (*s* (br.), 2NH), 2.32 (*dd*, *J*=4.6, 11.6, H_{exo}–C(3)), 1.69 (*d*, *J*=11.6, H_{endo}–C(3)). ^{13}C-NMR (50.1 MHz, $CDCl_3$): 141.67 (*s*), 139.78 (*s*), 137.71 (*d*), 134.98 (*d*), 128.21 (*d*), 128.14 (*d*), 127.51 (*d*), 127.41 (*d*), 127.23 (*d*), 127.01 (*d*), 84.83 (*d*), 83.01 (*s*), 78.56 (*d*), 69.89 (*d*), 69.50 (*d*), 46.13 (*t*). EI-MS: 305 ($[M+1]^+$, 9), 237 (15), 236 (69), 178 (10), 170 (11), 131 (20), 130 (35), 106 (100), 104 (19), 103 (17), 91 (23), 88.65 (14), 79 (15), 77 (18), 68 (12). IR (KBr): 3342, 3088, 3057, 3030, 2980, 2951, 2893, 2860, 1599, 1489, 1448. Anal. calcd for $C_{20}H_{20}N_2O$ (304.39): C, 78.92; H, 6.62; N, 9.20. Found: C, 78.68; H, 6.63; N, 9.28.

Data for (1*R*,4*R*)-(+)-**3**: m.p. 162°C (dec.). $[\alpha]^{23}_{589}$=+63.5 (c=0.28, $CHCl_3$) ^1H-NMR (360 MHz, $CDCl_3$): 7.30–7.15 (*m*, 10 arom. H), 6.54 (*dd*, *J*=5.8, 1.5, H–C(5)), 6.50 (*dd*, *J*=5.8, 1.5, H–C–(6)), 5.05 (*d* (br.), *J*=4.6, H–C(4)), 4.73 (*s* (br.), H–C(1)), 4.35, 4.09 (2*d*, *J*=8.4, H–C(4′), H–C(5′)), 2.38 (*s* (br.), 2NH), 2.24 (*dd*, *J*=4.9, 11.6, H_{exo}–C(3)), 1.73 (*d*, *J*=11.6, H_{endo}–C(3)). ^{13}C-NMR (50.1 MHz, $CDCl_3$): 141.03 (*s*), 140.54 (*s*), 138.58 (*d*), 133.96 (*d*), 128.46 (*d*), 128.20 (*d*), 127.62 (*d*), 127.22 (*d*), 126.86 (*d*), 85.62 (*d*), 83.62 (*d*), 83.50 (*s*), 78.99 (*d*), 70.48 (*d*), 69.51 (*d*), 45.93 (*t*). EI-MS: 305 (M^+, 9), 237 (15), 236 (68), 178 (10), 170 (11), 131 (20), 129 (35), 106 (100), 104 (19), 103 (17), 90 (23), 89 (14), 79 (15), 77 (18), 68 (12). IR (KBr): 3376, 3333, 3082, 3061, 3024, 3007, 2964, 2854, 2833, 2802, 2361, 2337, 1601. Anal. calcd for $C_{20}H_{20}N_2O$ (304.39): C, 78.92; H, 6.62; N, 9.20. Found: C, 78.68; H, 6.40; N, 9.07.

4.3. (1S,4S)-(−)-7-Oxabicyclo[2.2.1]hept-5-en-2-one (1S,4S)-(−)-**1**

A solution of (1*S*,4*S*)-**3** (3.64 g, 11.9 mmol) in 0.1 M H_3PO_4 (800 ml) was stirred for 30 min at r.t. and continuously extracted with Et_2O overnight. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. Bulb-to-bulb distillation gave (1*S*,4*S*)-(−)-**1** (1.04 g, 79%, >99% ee). B.p. 70°C/10 mmHg. The enantiomeric excess was determined by GC (β-cyclodextrin, 65% acetoxy, 100°C; (1*S*,4*S*)-(−)-**1**: t_{ret}=10.1 min, (1*R*,4*R*)-(+)-**3**: t_{ret}=10.6 min). $[\alpha]^{25}_{589}$ (1*S*,4*S*)-(−)-**3**=−1004 (c=1, $CHCl_3$); lit.[1c]: $[\alpha]^{25}_{589}$=−867 (c=2.4, CH_2Cl_2). The aqueous phase was treated with 2 M NaOH (pH=13) and extracted with CH_2Cl_2 to recover the diamine (*R*,*R*)-**2** (2.33 g, 92%).

4.4. (1R,4R)-(+)-7-Oxabicyclo[2.2.1]hept-5-en-2-one (1R,4R)-(+)-**1**

According to the procedure described for (1*S*,4*S*)-(−)-**1**, and starting from (1*R*,4*R*)-(+)-**3** (2.00 g, 6.5 mmol), afforded (1*R*,4*R*)-(+)-**1** (0.52 g, 72%, 95% ee). $[\alpha]^{25}_{589}$=+761 (c=1.8, $CHCl_3$); lit.[5a]: $[\alpha]^{25}_{589}$=+859.9 (c=2.4, CH_2Cl_2). The aqueous phase was treated with 2 M NaOH (pH=13) and extracted with CH_2Cl_2 to recover the diamine (*R*,*R*)-**2** (1.28 g, 92%).

4.5. Large scale procedure

The resolution of (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-**1**) was performed on a 15 g scale (unoptimized procedure). Due to the instability of the aminals, the hydrolysis was run immediately after isolation of each crop of diastereomerically pure (1*S*,4*S*)-(−)-**3** and (1*R*,4*R*)-(+)-**3**. Enantiomerically pure (1*S*,4*S*)-(−)-**1** (5.0 g, 33%, ≥99% ee) and (1*R*,4*R*)-(+)-**1** (4.4 g, 30%, ≥99% ee) were isolated.

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References

1. (a) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173–185; (b) Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348–5353; (c) Warm, A.; Vogel, P. *Helv. Chim. Acta* **1987**, *70*, 690–700; (d) Auberson, Y.; Vogel, P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1498–1499; (e) Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019–7032; (f) Jeganathan, S.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 1133–1142; (g) Reymond, J.-L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128–2135; (h) Moritz, V.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 5243–5244; (i) Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10587–10602; (j) de Guchteneere, E.; Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10603–10620; (k) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487–2496; (l) Ferritto, R.; Vogel, P. *Tetrahedron: Asymmetry* **1994**, *5*, 2077–2092; (m) Baudat, A.; Vogel, P. *J. Org. Chem.* **1997**, *62*, 6252–6260; (n) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V.; Ancerewicz, J.; Ferritto, R.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 8351–8359.
2. (a) Arjona, O.; Fernandez de la Pradilla, R.; Peres, S.; Plumet, J. *Tetrahedron* **1988**, *44*, 1235–1240; (b) Arjona, O.; Candilejo, A.; de Dios, A.; Fernandez de la Pradilla, R.; Plumet, J. *J. Org. Chem.* **1992**, *57*, 6097–6099; (c) Arjona, O.; de Dios, A.; Plumet, J.; Saez, B. *J. Org. Chem.* **1995**, *60*, 4932–4935; (d) Arjona, O.; de Dios, A.; Plumet, J.; Saez, B. *Tetrahedron Lett.* **1995**, *36*, 1319–1320.
3. (a) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* **1995**, *36*, 2067–2070; (b) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron* **1996**, *52*, 629–638.
4. (a) Vionnet, J.-P.; Renaud, P. *Helv. Chim. Acta* **1994**, *77*, 1781–1790; Renaud, P.; (b) Vionnet, J.-P. *J. Org. Chem.* **1993**, *58*, 5895–5896; (c) Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 3485–3488; (d) Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 7097–7100.

5. (a) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1865–1871; (b) Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729–736. Ronan, B.; Kagan, H. B. *Tetrahedron: Asymmetry* **1991**, *2*, 75–90; (c) Aggarwal, V. K.; Lightowler, M.; Lindell, S. D. *Synlett* **1992**, 730–732.
6. Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979–3982.
7. Black, K. A.; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 1612–1615.
8. (a) Wagner, J.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1988**, *71*, 624–630; (b) Renaut, P.; Millet, S.; Sepulchre C.; Theveniaux, J.; Barberousse, V.; Jeanneret, V.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 2043–2052.
9. Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431–2434.
10. (a) Corey, E. J.; Pikul, S. *Org. Synth.* **1993**, *71*, 22–29; (b) Corey, E. J.; Lee, D. H.; Sarsshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3–6.