187. Optical Resolution of 7-Oxabicyclo[2.2.1]hept-2-ene Derivatives. Diastereoselectivity in the Formation of Cyanohydrine-Brucine Complexes

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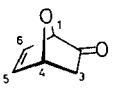
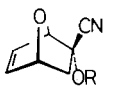
Summary

A new, practical method for the optical resolution of bicyclic ketones is illustrated by the preparation of (+)-(1*R*,4*R*)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((+)-**1**) and (+)-(1*R*,2*S*,4*R*)-2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl acetate ((+)-**4**). It involves the diastereoselective formation of a brucine complex with the corresponding cyanhydrine mixture.

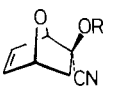
Derivatives of 7-oxabicyclo[2.2.1]heptane have proved to be convenient starting materials in the synthesis of a large body of natural products and materials of biological interest [1]. Some derivatives have also been shown to exhibit antitumor [2] or antiinflammatory activity [3]. We recently reported the preparation of two optically pure 7-oxabicyclo[2.2.1]heptane derivatives, (+)-**1** and (+)-**2** [4]. Systems such as these



(+)-**1**



R = Camphanyl **2**
R = Ac **3**
R = H **5**



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can be viewed as 'naked sugars' since positions C(3), C(5), and C(6) can be stereospecifically functionalized with a variety of substituents; electrophilic additions to the C(5), C(6) double bond are highly stereoselective [5] [6], and electrophilic substitution of a H-atom at C(3) in **1** (and other related ketones) can also be highly stereoselective under either thermodynamic or kinetic control [7]. *Toda & Tanaka* recently reported [8] a novel optical-resolution method applicable to tertiary acetylenic alcohols and cyanohydrins which involves complexation with brucine. Disclosed below is the successful application of this method to the optical resolution of 7-oxabicyclo[2.2.1]hept-5-ene-2-one ((±)-**1**) and the *endo*-carbonitrile (±)-**4**. A substantially improved synthesis of the racemic materials (±)-**1** and (±)-**3** [9] is also reported.

The ZnI_2-catalyzed *Diels-Alder* addition [4] of furan to α-acetoxyacrylonitrile (= 1-cyanovinyl acetate) gave a 4:1 mixture (90% crude) of the *exo-vs. endo*-carbonitriles (±)-**3** and (±)-**4** [9]. Isomerically pure (±)-**3** (54–59%) could be crystallized directly from the crude reaction product, and a 3:4 mixture of (±)-**3** and (±)-**4** (21–26%) was obtained from the filtrate. Treatment of a mixture (±)-**3**/(±)-**4** in MeOH with a cata-

lytic amount of NaOMe produced a solution containing an equilibrating mixture of the corresponding cyanohydrins (±)-**5** and (±)-**6** and a trace of ketone (±)-**1**. Addition of excess formalin to this solution gave 7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-**1**) in 90% yield.

When 1 equiv. of brucine was added to the above methanolic solution of cyanohydrins, a white complex precipitated (20°, 15 h, 63.7%). Treatment of this material with Ac_2O or AcCl ($CHCl_3$, pyridine, 20°, 24 h) furnished a 7:93 mixture of acetates **3** and **4** (80–90%). When, instead, the above solution of equilibrated cyanohydrins **5** and **6** was simply evaporated to dryness and acylated as above, a 1:2 mixture of **3** and **4** was produced. This demonstrates the diastereoselectivity in the formation of the cyanohydrin-brucine complex, and also shows that under these conditions, acylation of the cyanohydrin liberated from this complex is faster than the equilibration **5**⇄**6**. Concentration of the mother liquors from the initial cyanohydrin-brucine complexation reaction gave a solid which produced a 2:3 mixture of acetates **3** and **4** when subjected to the same acylating conditions.

The optically active ketone **1** could be obtained from the above mixtures of acetates **3** and **4**, or directly from the cyanohydrin-brucine complex (MeOH, NaOMe, formalin). Thus, the initially precipitated complex gave (+)-**1** (90%) with *ca.* 44% enantiomeric excess (e.e.), and the mother liquors from this complexation afforded (–)-**1** (71%, *ca.* 70% e.e.). These and subsequent enantiomeric ratios were determined by ^{1}H-NMR analysis of the sample in the presence of the optically active shift reagent tris[3-(heptafluoropropyl-hydroxymethylidene)-D-camphorato]europium (III) ($Eu(hfbc)_3$), or through polarimetry[1]).

Two successive recrystallizations of the cyanohydrin-brucine complex from MeOH (21% overall), followed by acylation as described above (95%), yielded (+)-**4**, contaminated with only *ca.* 3% of **3** (^{1}H-NMR analysis, 80 MHz). Crystallization of this material provided isomerically pure (+)-**4** (71%) with an e.e. > 99% by ^{1}H-NMR analysis ($Eu(hfbc)_3$, C_6D_6, 360 MHz). From this sample of (+)-**4** was also derived optically pure (+)-**1** (93%). When the twice recrystallized sample of cyanohydrin-brucine complex was treated to give directly (+)-**1**, the e.e. was *ca.* 90%, presumably diminished because the small amount of **5** within the complex is of the (1*S*, 2*R*, 4*S*)-configuration and therefore leads to (–)-**1**.

All mother liquors from the initial complexation reaction and subsequent recrystallizations can be combined and acylated in high yield. The resulting mixture of **3** and **4** can then be simply heated to induce *retro*-cycloaddition and allow for recycling of the α-acetoxyacrylonitrile and furan. The mixture of cyanohydrin (±)-**5** and (±)-**6** is also formed by adding 1 equiv. of NaCN to a methanolic solution of (±)-**1**, and thus the experiments reported here may present a practical method for the optical resolution of bicyclic ketones[2]). Particularly useful is the ability to isolate the *endo*-carbonitrile **4** in its optically pure form. This is the minor isomer obtained from the *Diels-Alder* additions of furan to α-acetoxyacrylonitrile and (–)-1-cyanovinyl camphanate [4].

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[1]) The conditions were changed from those reported [4] to improve the precision of these measurements.

[2]) For other methods to achieve the optical resolution of ketones see [10].

Experimental Part

General Remarks. See [4].

*(±)-2-*exo- *and (±)-2-*endo-*Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl Acetates ((±)-***3** *and (±)-***4***).* A solution of α-acetoxyacrylonitrile (1-cyanovinyl-acetate; *Fluka*; 55.5 g, 0.5 mol) and ZnI_2 (48.0 g, 0.15 mol, *Fluka*) in furan (68 g, 1 mol) was stirred in the dark at 20° in a stoppered flask. Some of the ZnI_2 remained suspended in the light yellow solution after 24 h, at which time more furan (34 g, 0.5 mol) was added. The mixture was stirred for an additional 5 days before it solidified. The white solid was dissolved in a mixture of Et_2O (1000 ml), H_2O (500 ml), and sat. aq. NaCl (500 ml), and after separation of the layers, the aq. fraction was extracted with Et_2O (100 ml, 5 times). The combined Et_2O extracts were washed with 5% aq. $NaHCO_3$ (100 ml, 4 times) and sat. aq. NaCl (100 ml, 4 times), then dried ($MgSO_4$), filtered, and concentrated to yield a yellow oily solid (73.85 g). The aq. solutions were combined and extracted again with Et_2O (100 ml, 3 times) which was then washed, dried, and concentrated as above to yield additional product (6.8 g; in total: 80.65 g (90% crude)). Three recrystallizations from Et_2O (225 ml) and petroleum ether (50 ml) at –20° gave 48.2 g (54%) of isomerically pure (±)-**3**, m.p. 65–6° (spectroscopic data, see [9]). The mother liquor were concentrated and flash chromatographed on silica gel to give 22.9 g (25%) of a 3:4 mixture of (±)-**3** and (±)-**4.**

*(±)-7-Oxabicyclo[2.2.1]hept-5-en-2-one ((±)-***1***).* To a solution of (±)-**3**/(±)-**4** (14.64 g, 81.8 mmol) in dry MeOH (75 ml) stirred at 20° under N_2 was added MeONa (30% in MeOH, 5.4M; 0.75 ml, 4.5 mmol). After 2 h, the resulting equilibrium mixture of (±)-**1** and the corresponding cyanohydrins (±)-**5** and (±)-**6** was treated with formalin (25 ml, 40% solution in H_2O; 10.8 g, 0.35 mol) and then stirred for 1 additional h. The mixture was diluted with H_2O (75 ml), sat. aq. NaCl (75 ml), and CH_2Cl_2 (50 ml). The layers were separated, and the aq. fraction was extracted with CH_2Cl_2 (20 ml, 7 times). The combined org. fractions were washed with sat. aq. NaCl (25 ml, 5 times), dried ($MgSO_4$), and filtered. Concentration by distillation at atmospheric pressure yielded at light yellow liquid which gave, after bulb-to-bulb distillation (90 °C, 15 Torr), a colorless oil (8.05 g, 89.5%) identical with (±)-**1** described in [9].

*(+)-(1*R*,2*S*,4*R*)-2-Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl Acetate ((+)-***4***).* To a solution of crude (±)-**3**/(±)-**4** (8.95 g, 50 mmol) in MeOH (100 ml) stirred under N_2 at 20° was added MeONa (30% in MeOH, 5.4M; 0.25 ml, 1.35 mmol). Saponification was completed after 4 h, at which time brucine (19.75 g, 50 mmol) was added to the solution. During this addition, a white precipitate began to form. The mixture was stirred overnight at 20° and then filtered to give a white solid which was washed with Et_2O (100 ml) and dried *in vacuo* to give 16.95 g (*sample A;* 38.2 mmol, 63.7%) of complex. The filtrate was concentrated and gave 10.9 g of yellow solid (*sample B*). The crude cyanohydrin-brucine complex (*sample A;* 16.82 g, 37.9 mmol) was dissolved in a minimum amount of hot MeOH (250 ml) from which crystallization took place on colling to 20° giving 9.73 g (18.3 mmol) of crystallization solid. The latter was again recrystallized from hot MeOH (160 ml) to give, after filtration, washing with Et_2O and drying, 5.56 g (10.44 mmol, 21%) of pure complex (*sample C*). To a solution of *sample C* (1.33 g, 2.5 mmol) in $CHCl_3$ (75 ml) stirred at 20° under N_2 was added Ac_2O (0.765 g, 7.5 mmol) and pyridine (0.59 g, 7.5 mmol). The solution was stirred for 24 h in the dark and then washed with 1N aq. HCl (20 ml, 3 times) and 5% aq. $NaHCO_3$ (10 ml, 2 times). After drying ($MgSO_4$), the solution was evaporated *in vacuo* and flash chromatographed on silica gel (EtOAc/Et_2O/pentane 1:1:5) to give 0.425 g (2.37 mmol, 95%) of a 97:3 mixture of **4**/**3** (by ^{1}H-NMR, 80 MHz). Recrystallization from Et_2O/petroleum ether 1:1 gave 0.32 g (71.5%) of crystalline (+)-**4**, m.p. 57.5–58°. $[\alpha]_{589}^{25} = +57.9$, $[\alpha]_{578}^{25} = +60.9$, $[\alpha]_{546}^{25} = +69.8$, $[\alpha]_{436}^{25} = +125$, $[\alpha]_{365}^{25} = +215$, ($c = 1.69$ mg/ml, $CHCl_3$). IR ($CHCl_3$): 2242, 1760, 1374, 1318, 1232, 1066, 1022. ^{1}H-NMR (360 MHz, $CDCl_3$): 6.74 (*dd*, $J = 6.0, 1.5$) and 6.54 (*dd*, $J = 6.0, 2.0$, H–C(5), H–C(6)); 5.31 (*m*, H–C(1)); 5.18 (*dm*, $J = 4.25$, H–C (4)); 2.31 (*d*, $J = 13.0$, H_{endo}–C(3)); 2.23 (*dd*, $J = 13.0, 4.25$, H_{exo}–C(3)); 2.18 (*s*, CH_3). ^{13}C-NMR (90 MHz, $CDCl_3$): 169.5 (*s*), 141 (*dm*, $^1J_{C,H} = 178$) and 132 (*dm*, $^1J_{C,H} = 181$, C(5), C(6)); 117.5 (*s*, CN); 83.9 (*dm*, $^1J_{C,H} = 172$, C(1)); 78.6 (*dm*, $^1J_{C,H} = 168$, C(4)); 74 (*s*, C(2)); 41.9 (*t*, $^1J_{C,H} = 141$, C(3)); 20.7 (*q*, $^1J_{C,H} = 131$, CH_3). MS (CI, isobutane): 180 (7, $M + 1$), 153 (9), 149 (6), 140 (7), 120 (11), 112 (100). Anal. calc. for $C_9H_9NO_3$ (179.18): C 60.33, H 5.06; found: C 60.42, H 5.15.

A solution of this material ((+)-**4**; 10 mg) in C_6D_6 (0.4 ml) was treated with Eu(hfbs)$_3$ (10 mg), bubbled with a stream of N_2 and analyzed by ^{1}H-NMR (360 MHz). Under these conditions, the acetoxy signals of the enantiomers are clearly separated (by 4 Hz), and this sample showed only one peak in this region (> 99% e.e.).

*(+)-(1*R*,4*R*)-7-Oxabicyclo[2.2.1]hept-5-en-2-one((+)-***1***): Method A.* A sample of (+)-**4** (200 mg; 1.12 mmol; > 99% e.e.) was transformed into (+)-**1** following the synthetic procedure for (±)-**1**. The oil obtained (113 mg, 93%), $[\alpha]_{589}^{25} = +959$, $[\alpha]_{578}^{25} = +1008$, $[\alpha]_{546}^{25} = +1207$, $[\alpha]_{436}^{25} = +2752$, $[\alpha]_{365}^{25} = +7421$ ($c = 0.121$ mg/ml, $CHCl_3$), had spectral characteristics identical with those reported [4].

Method B. To a suspension of the recrystallized brucine complex (*sample C*; 2.66 g, 5 mmol) in dry MeOH (50 ml) stirred at 20° was added NaOMe (30% solution in MeOH, 5.4M; 0.75 ml, 0.4 mmol) and formalin (40% solution in H_2O; 1.85 ml, 25 mmol). After several min, the suspended complex was solubilized, and stirring was continued for 1.5 h. The solution was diluted with sat. aq. NaCl (150 ml) and 1N aq. HCl (50 ml) and then extracted with CH_2Cl_2 (25 ml, 10 times). The extracts were washed with 1N aq. HCl (20 ml, 2 times), dried ($MgSO_4$), filtered, and concentrated by distillation at atmospheric pressure to give a yellow oil. During the concentration, a white precipitate formed which was filtered from the solution after adding a small amount of petroleum ether. The resulting oil was bulb-to-bulb distilled (90°–100°, 15 Torr) and gave 0.51 g (93%) of a clear, colorless liquid, $[\alpha]_{589}^{25} = +874$, $[\alpha]_{578}^{25} = +919$, $[\alpha]_{546}^{25} = +1104$, $[\alpha]_{436}^{25} = +2489$, $[\alpha]_{365}^{25} = +6696$, ($c = 0.135$ mg/ml, $CHCl_3$). Other spectral characteristics were identical with those reported [4]. A solution of this material (10 mg) in C_6D_6 (0.4 ml) was treated with Eu(hfbc)$_3$ (8 mg), bubbled with a stream of N_2, and analyzed by 360-MHz-^{1}H-NMR. Under these conditions, both the H_{exo}–C(3) and H_{endo}–C(3) peaks are split for enantiomers (by 0.19 and 0.10 ppm, resp.), and this sample showed an enantiomeric excess of 90%.

*(–)-(1S,4S)-7-Oxabicyclo[2.2.1]hept-5-en-2-one((–)-***1***).* The above synthetic procedure was repeated using the crude complex in the filtrate from the initial cyanohydrin-brucine complexation (*sample B*). The colorless oil obtained (71%), $[\alpha]_{589}^{25} = -695$, $[\alpha]_{578}^{25} = -732$, $[\alpha]_{546}^{25} = -878$, $[\alpha]_{436}^{25} = -2006$, $[\alpha]_{365}^{25} = -5402$ ($c = 0.164$ mg/ml, $CHCl_3$), was subjected to an ^{1}H-NMR analysis (C_6D_6, Eu(hfbc)$_3$, 360 MHz) which indicated an e.e. of 70%. Other spectral characteristics were identical with those of the racemic material [9].

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