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Synthesis and Alcoholysis of α-Alkylated Cyclopentane and Cyclohexane Fused Succinic Racemic Anhydrides in the Presence of Chiral Bases

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Abstract: Bicyclic succinic anhydrides alkylated at the α-position have been prepared and submitted to alcoholysis in the presence of alkaloid bases. Anhydrides with a cyclopentane fused ring, open only from the less hindered side, generating monoesters of >80 % *ee*, whereas cyclohexane fused anhydrides undergo parallel kinetic resolution, producing both regioisomeric monoesters.

Keywords: cyclic anhydrides, stereoselective alcoholysis, quinine, kinetic resolution, parallel kinetic resolution.

INTRODUCTION

THE enantioselective alcoholysis of cyclic *meso*-anhydrides catalyzed by cinchona alkaloids[1] has been confirmed as a powerful tool in the syntheses of enantiomerically enriched substances. Derived β- and γ-amino acids are either already biologically active compounds (Cispentacin,[2] Pregabalin,[3] Baclofen[4]) or potential building blocks in the synthesis of more complex molecules (Biotin,[5] Brefeldin[6]). Whereas desymmetrization of *meso*-anhydrides has been extensively studied, there are only few trials to perform the same reaction on racemic anhydrides. Thus, Deng[7] studied opening of α-methyl succinic anhydride, whereas Bolm[8] studied opening of bicyclic succinic anhydride methylated at β-position. Both substrates underwent parallel kinetic resolution (PKR) with good to exellent enantioselectivities. With the aim of possible synthesis of new unnatural chiral β-amino acid derivatives as building blocks for potential pharmacons, β-lactams or peptide analogues[9] we decided to examine the course of this reaction on more hindered substrates – bicyclic succinic anhydrides alkylated at α-position.

EXPERIMENTAL SECTION

General Methods

Reactions were conducted under the argon atmosphere. All reagents and solvents were purchased from commercial sources and used without purification. ^{1}H and ^{13}C NMR were recorded on Bruker AV 300 spectrometer. Chemical shifts (δH and δC) are quoted in parts per million (ppm), referenced to TMS. IR spectra were recorded on Bruker ABB Bomem MB102 spectrometer. Melting points were determined on Electrothermal 9100 apparatus in open capillaries and are not corrected. For the chemical purity determination, and monitoring of the progress of the reactions Nucleosil 100-5 C18 column was used (50 to 100 % MeOH in 20 min).

Preparation of Anhydrides 11–14

To the solution of diethyl-cyclopentane-1,2-dicarboxylate (**1**) (1.12 g, 5 mmol) dissolved in 20 mL of *n*-hexane 1.3 eqv. of lithium diisopropylamide (1.0 M sol. in THF/hexanes) have been added at –78 °C. Upon 30 min of stirring at the same temperature alkyl halogenide was added (2 eqv.).

Resulting yellow suspension was gradually warmed to room temperature (rt) during 2 h and then was treated with 20 mL of saturated NH_4Cl solution. Organic layer was separated and aqueous layer was extracted with diisopropylether (3 × 20 mL). Combined organic layers were evaporated and oily residue was dissolved in 30 mL of 70 % EtOH containing 250 mg of KOH. The reaction mixture was stirred for 3 h at rt; most of ethanol was evaporated (without heating) and remainder was extracted with CH_2Cl_2. Evaporation yielded mixture of *cis* and *trans* diesters **2–6** containing 1–2 % of dialkylated products.

Crude diesters **2–6** were dissolved in 70 % EtOH (1g/60 mL), 10 eqv of KOH were added and the solution was refluxed for 48 h. Ethanol was evaporated and residue was extracted with CH_2Cl_2 (3 × 30 mL). Aqueous layer was acidified to pH = 2 with diluted HCl and extracted with diethyl ether (4 × 30 mL). Evaporation yielded mixtures of *cis* and *trans* diacids **7–10**.

The solution of diacid in propanoic anhydride (0.1 g/mL) was heated at 140 °C for 48 h. Anhydrides **11–14** were isolated by distillation on Kugelrohr apparatus; first at 14 mm Hg to remove propanoic anhydride and then products at 0.5 mm Hg.

11: ^{1}H NMR ($CDCl_3$, 300 MHz), δ/ppm: 1.49 (s, 3H), 1.51–2.33 (m, 6H), 3.03 (dd, 1H, J_1= 9.5 Hz, J_2= 1.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ/ppm: 22.33, 25.94, 28.73, 31.62, 40.01, 52.25, 173.93, 177.48. IR (KBr), ν_{max}/cm^{-1}: 2971, 2873, 1854, 1779, 1453, 1223, 1057, 979, 936, 911.

12: ^{1}H NMR ($CDCl_3$, 300 MHz), δ/ppm: 0.93 (t, 3H, J = 7.4 Hz), 1.40–1.70 (m, 3H), 1.77–2.01 (m, 3H), 2.16–2.29 (m, 2H), 3.02 (d, 1H, J = 9.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ/ppm: 9.76, 25.62, 28.89, 31.78, 38.14, 49.18, 58.20, 174.21, 177,12. IR (KBr), ν_{max}/cm^{-1}: 2971, 2944, 2877, 1860, 1780, 1456, 1237, 1214, 1047, 1004, 950, 924.

13: ^{1}H NMR ($CDCl_3$, 300 MHz), δ/ppm: 1.48–1.61 (m,1H), 1.71–2.09(m, 3H), 2.22–2.39 (m, 3H), 2.67–2,74 (m, 1H), 3.13 (d, 1H, J = 9.5 Hz), 5.19 (d,1H, J = 5.1 Hz), 5.24 (s, 1H), 5.65–5.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ/ppm: 25.66, 31.69, 38.06, 39.72, 49.05, 57.26, 121.05, 131.51, 173.89, 176.73. IR (KBr), ν_{max}/cm^{-1}: 2967, 2875, 1852, 1779, 1454, 1233, 1206, 1043, 1002, 945, 923.

14: mp = 60–61 °C. ^{1}H NMR ($CDCl_3$, 300 MHz), δ/ppm: 1.48–1.61 (m, 1H), 1.71–2.09 (m, 3H), 2.22–2.39 (m, 3H), 2.67–2.74 (m, 1H), 3.13 (d, 1H, J = 9.5 Hz), 5,19 (d, 1H, J = 5.1 Hz), 5.24 (s, 1H), 5.65–5.76 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ/ppm: 25.66, 31.69, 38.06, 39.72, 49.05, 57.26, 121.05, 131.51, 173.89, 176.73. IR (KBr), ν_{max}/cm^{-1}: 2968, 2872, 1844, 1777, 1452, 1229, 1045, 947, 702.

Preparation of Anhydrides 22 and 23

To the suspension of $NaBH_4$ (2.5 g, 65 mmol) in 15 mL of THF, the solution of anhydride **15** (10 g, 65 mmol) in 50 ml of THF was added at 0 °C in 45 min. The reaction mixture was stirred at rt for 2 h; 25 mL of 6 M HCl was added and stirring was continued for 30 min. Most of THF was evaporated, 150 mL of H_2O was added and product was extracted with MTBE (3 × 50 mL). Crude lactone **16** was purified by vacuum distillation (0.2 mm Hg/100–125 °C). Yield: 4.5 g (50 %).

To the solution of LiHMDS (1 M in hexanes, 9.0 mmol, 9.0 mL) in 10 mL toluene the solution of lactone **16** in toluene (1.25 g, 9.0 mmol; 3 mL of toluene) was added at –78 °C. The reaction mixture was warmed to rt, stirred for 1 h and alkyl halogenide (1 eqv.) was added. Upon stirring overnight at rt, 20 mL of NH_4Cl were added. Layers were sepparated and aqueous layer was extracted with EtOAc (2 × 20 mL). Combined organic solutions were washed with brine, dried and evaporated to achieve alkyl lactones **17–19** in 80–90 % yield.

Alkyl lactones were dissolved in acetic acid (~1 g/250 mL) and solution of CrO_3 (2. eqv.) in 50 % H_2SO_4 (1 g/5 mL) was added. The reaction mixture was was stirred at rt for 10–15 days, acetic acid was evaporated (vacuum, gentle heating). Saturated NaCl solution (100 mL) was added to the residue and extracted with EtOAc (4 × 50 mL). Diacids **20** and **21** were obtained in 50 % yield.

The solution of diacid in propanoic anhydride (0.1 g/mL) was heated at 140 °C for 48 h. Anhydrides **22** and **23** were isolated by distillation on Kugelrohr apparatus; first at 14 mm Hg to remove propanoic anhydride and then products at 0.5 mm Hg.

22: ^{1}H NMR ($CDCl_3$, 300 MHz), δ/ppm: 1.43 (s, 3 H), 1.58–1,.72 (m, 7H), 2.08–2.14 (m, 1H), 2.82–2,85 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ/ppm: 20.47, 20.62, 21.24, 21.98, 32.85, 44.54, 47.22, 172.12, 176.13. IR (KBr), ν_{max}/cm^{-1}: 2944, 2864, 1859, 1841, 1782, 1458; 1249, 1191, 950, 927.

23: ^{1}H NMR ($CDCl_3$, 300 MHz), δ/ppm: 0.99 (t, 3H, J = 7.4 Hz), 1.43–1.89 (m, 9H), 1.99–2.06 (m, 1H), 2.95 (t, 1H, J = 5.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz), δ/ppm: 9.04, 20.63, 21.71, 21.95, 27.42, 31.43, 43.71, 48.97, 172.81, 175.38. IR (KBr), ν_{max}/cm^{-1}: 2968; 2943; 2862; 1858; 1779; 1460; 1231; 1187; 972; 916.

Alcoholysis of Anhydrides 11–14

To the solution of anhydride in toluene (c = 0.02 M), cinnamyl alcohol (1 eqv.) and catalyst (1.1 eqv. of quinine or quinidine; 15 mol % or 20 mol % $(DHQD)_2AQN$) were added and the reaction mixture was stirred at –30 °C for 40 h. *p*-Methoxybenzyl alcohol (3 eqv.) and Et_3N (3 eqv.) were added and stirring was continued for 5 h at rt. Reaction

mixture was washed with 1 M HCl (2 ×) and then evaporated. Oily residue was dissolved in 2 % K_2CO_3 and extracted with EtOAc (5 ×). Aqueous phase was acidified with 1M HCl to pH = 1–2 and extracted with EtOAc (3 ×). Small amounts of products, for the analysis, were separated by HPLC.

24: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.34 (s, 1H), 1.54–2.27 (m, 6H), 2.62 (t, J = 8.3 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H), 6.17 (dt, J_1 = 15.9 Hz, J_2 = 6.4 Hz, 1H), 7.08–7.31 (m, 5H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$), δ/ppm: 22.3, 24.7, 28.3, 37.5, 51.9, 53.9, 64.7, 122.8, 126.2, 127.4, 128.1, 133.4, 135.8, 137.2, 182.5.

25: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.96 (t, J = 7.5 Hz, 3H), 1.62–2.37 (m, 8H), 2.84 (t, J = 7.7 Hz, 1H), 4.74(dd, J_1 = 6.4 Hz, J_2 = 1.0 Hz, 2H), 6.29 (dt, 1H, J_1 = 15.8 Hz, J_2 = 6.3 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 7.25–7.43 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$), δ/ppm: 8.9, 22.2, 28.4, 30.4, 32.9, 52.2, 57.5, 64.7, 122.8, 126.0, 126.1, 127.4, 128.1, 133.5, 174.1, 179.6 ppm.

26: ^{1}H NMR (300 MHz, DMSO-d_6), δ/ppm: 1.57–2.37 (m, 8H), 2.77 (t, J = 7.7 Hz, 1H), 4.66 (d, J = 5.8 Hz, 2H), 5.03–5.11 (m, 2H), 5.73-5.82 (m, 1H), 6.33 (dt, J_1 = 16.0 Hz, J_2 = 5.9 Hz, 1H), 7.21–7.46 (m, 5H), 12.30 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ/ppm: 22.7, 28.7, 33.9, 41.8, 51.5, 56.4, 64.7, 118.7, 124.4, 126.9, 128.4, 129.1, 133.1, 134.9, 136.5, 173.7, 176.5.

27: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.48–2.20 (m, 6H), 2.84 (t, J = 7.6 Hz, 1H), 3.06–3.22 (m, 2H), 4.76 (d, J = 6.4 Hz, 2H), 6.29 (dt, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 7.13–7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 22.4, 27.9, 33.9, 41.2, 50.1, 57.7, 65.4, 123.2, 126.7, 126.9, 128.3, 128.6, 130.5, 130.7, 134.1, 136.8, 136.9, 179.5, 182.3.

28: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.43 (s, 3H), 1.64–2.32 (m, 6H), 2.70 (t, J = 8.3 Hz, 1H), 3.80 (s, 3H), 5.03 (dd, J_1 = 12.0 Hz, J_2 = 4.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.25–7.28 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$), δ/ppm: 22.3, 24.7, 28.2, 37.6, 51.9, 53.8, 54.7, 113.4, 127.6, 129.4, 158.9, 173.3, 181.9.

29: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.91 (t, J = 7.4 Hz, 3H), 1.58–1.72 (m, 3H), 1.81–2.04 (m, 4H), 2.28–2.31 (m, 1H), 2.77 (t, J = 7.6 Hz, 1H), 3.79 (s, 3H), 5.01 (s, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.25–7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 9.56, 22.78, 28.29, 30.91, 33.49, 52.67, 55.33, 57.61, 66.31, 113.95, 128.23, 130.07, 159.58, 174.28, 181.23.

30: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.59–1.89 (m, 3H), 2.00–2.07 (m,2H), 2.19–2.28 (m, 1H), 2.37–2.44 (m, 1H), 2.54–2.61 (m, 1H), 2.82 (t, 7.9 Hz, 1H), 3.79 (s, 3H), 4.97–5.11 (m, 4H), 5.71–8.83 (m, 1H), 6.85–6.90 (m, 2H), 7.24–7.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 22.8, 28.7, 34.2, 41.6, 51.8, 55.3, 56.3, 66.3, 113.9, 118.9, 128.1, 129.9, 133.5, 159.5, 173.8, 181.1.

31: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.49–1.65 (m, 1H), 1.75–1.83 (m, 2H), 1.96–2.19 (m, 3H), 2.79 (t, J = 8.6 Hz, 1H), 3.06 (d, J = 13.5 Hz, 1H), 3.17 (d, J = 12.9 Hz, 1H), 3.79 (s, 3H), 5.07 (s, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 6.9 Hz, 2H), 7.22–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 22.0, 27.9, 33.7, 41.7, 50.7, 55.3, 57.8, 66.4, 113.9, 126.9, 128.2, 128.3, 130.1, 130.6, 136.9, 159.6, 173.9, 181.1.

Alcoholysis of Anhydrides 22 and 23

To the solution of anhydride in toluene (c = 0.02 M), cinnamyl alcohol (1 eqv.) and catalyst (1.1 eqv. of quinine or quinidine; 15 mol % or 20 mol % $(DHQD)_2AQN$) were added and the reaction mixture was stirred at –30 °C (+4 °C for **23**) for 70 h. Reaction mixture was washed with 1 M HCl (2x) and then evaporated. Oily residue was dissolved in 2 % K_2CO_3 and extracted with EtOAc (5 ×). Aqueous phase was acidified with 1M HCl to pH = 1–2 and extracted with EtOAc (3 ×). Small amounts of products, for the analysis, were separated by HPLC.

32: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.34 (s, 3H), 1.42–1.54 (m, 5H), 1.89–1.94 (m, 2H), 2.13–2.14 (m, 1H), 2.54–2.58 (m, 1H), 4.73 (d, J = 6.3 Hz, 2H), 6.24 (dt, J_1 = 15.9 Hz, J_2 = 6.3 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$), δ/ppm: 22.0, 23.8, 25.2, 25.4, 34.0, 44.1, 49.6, 65.4, 123.2, 126.7, 128.1, 128.7, 134.1, 136.4, 177.1, 179.1.

33: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.89 (t, J = 7.3 Hz, 3H), 1.30–1.90 (m, 10H), 2.73–2.81 (m, 1H), 4.77 (d, J = 6.5 Hz, 2H), 6.27 (dt, J_1 = 16.0 Hz, J_2 = 6.3 Hz, 1H), 6.66 (d, J = 15.8 Hz, 1H), 7.24–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 8.3, 21.5, 23.5, 25.9, 28.9, 29.7, 48.0, 48.2, 65.7, 122.7, 127.7, 128.2, 128.6, 134.6, 136.1, 175.9, 182.9.

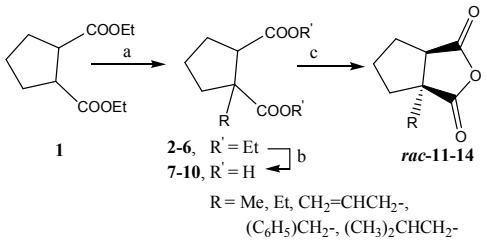
34: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 1.33 (s, 3H), 1.37–1.57 (m, 5H), 1.87–1.97 (m, 2H), 2.14–2.19 (m, 1H), 2.59-2.63 (m, 1H), 4.75 (d, J = 6.3 Hz, 2H), 6.26 (dt, J_1 = 15.9 Hz, J_2 = 6.4 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 7.22–7.32 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$), δ/ppm: 21.8, 23,8, 25.1, 25.7, 33.8, 44.1, 49.5, 65.5, 123.1, 126.7, 128.1, 128.7, 134.3, 136.3, 174.8, 181.4.

35: ^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 0.88 (t, J = 5.3 Hz, 3H), 1.26–2.06 (m, 10H), 2.74–2.84 (m, 1H), 4.76 (d, J = 6.2 Hz, 2H), 6.26 (dt, J_1 = 15.9 Hz, J_2 = 6.6 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 7.23–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 8.3, 21.2, 22.6, 24.8, 27.5, 28.6, 46.7, 47.1, 65.6, 122.8, 126.7, 128.1, 128.6, 134.4, 136.2, 177.4, 181.1.

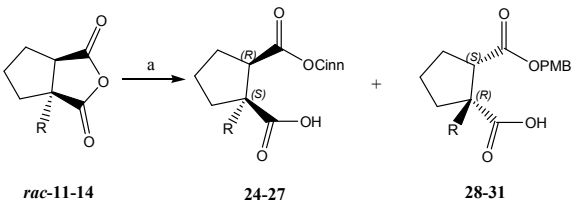
RESULTS AND DISCUSION

Two series of cyclic anhydrides were prepared: first one possessing cyclopentane ring fused to succinic anhydride and the second one with fused cyclohexane ring. Anhydrides **11–14** were prepared starting from diester **1** which was alkylated at the α-position using LDA as the base (Scheme 1, Table 1). *n*-Hexane as the solvent was found to be much better than THF with respect to the control of the reaction – at about 70 % conversion only 1–2 % of dialkylated product was formed. Remaining diester **1** was easily removed from the reaction mixture by hydrolysis at rt leaving monoalkylated diesters **2–6**, together with a small amount of dialkylated product. Hydrolysis of **2–6** required higher temperature and prolonged reaction time while dialkylated byproduct remains unhydrolysed. Finally, diacids **7–10** (*cis/trans* mixtures, Table 1) were converted to *cis*-anhydrides **11–14** by the action of propionic anhydride.

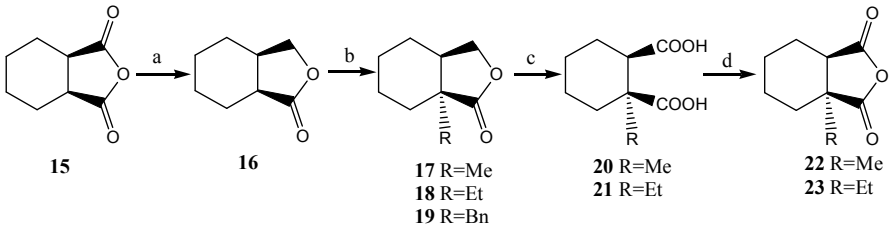
Unfortunately, attempted alkylation of cyclohexane-1,2-dicarboxylic acid diester resulted in an inseparable mixture of mono and dialkylated products, consequently different approach to these compounds was applied. Lactone **16**, obtained by the reduction of anhydride **15** with $NaBH_4$ and



Scheme 1. Synthesis of α-alkylated cyclopentane-fused succinic anhydrides. Reagents and conditions: (a) *n*-hexane, LDA, –78 °C (30 min); RX, –78 °C (45 min), rt (90 min); 70 % EtOH, KOH, rt (3 h); (b) 70 % EtOH, KOH, reflux (20 h), for R = Et$(CH_3)_3$SiI at 100 °C (21 h); (c) $(EtCO)_2O$, 135 °C (24 h).



Scheme 3. Kinetic resolution of α-alkylated cyclopentane-fused succinic anhydrides. Reagents and conditions: (a) toluene, anhydride (5 mg, c = 0.02 M), base, cinnamyl alc. (1 eqv.), –30 °C (40 h); then *p*-methoxybenzyl alc. (3 eqv.), Et_3N, rt (5 h).



Scheme 2. Synthesis of α-alkylated cyclohexane-fused succinic anhydrides. Reagents and conditions: (a) THF, $NaBH_4$, 0 °C (2 h); HCl, 50 %; (b) toluene, LiHMDS, -78 °C (30 min); RX, rt (15 h), 80–95 %; (c) AcOH, CrO_3/H_2SO_4(aq), rt (10 days), 50 %; (d) $(EtCO)_2O$, 135 °C (24 h), 75–85 %.

Table 1. Synthesis of anhydrides *rac*-**11–14**

RX	diester **2** – **6**			acid **7** – **10**			anhydride **11** – **14**	
		yield / %	*cis* : *trans*[a]		yield / %	*cis* : *trans*[a]		yield / %
CH_3I	**2**	54	15 : 85	**7**	82	23 : 77	*rac*-**11**	67
CH_3CH_2Br	**3**	12	32 : 68	**8**	87	53 : 47	*rac*-**12**	68
CH_2=$CHCH_2I$	**4**	45	52 : 48	**9**	98	58 : 42	*rac*-**13**	75
$(C_6H_5)CH_2Br$	**5**	52	67 : 33	**10**	92	70 : 30	*rac*-**14**	62
$(CH_3)_2CHCH_2Br$	**6**	4	15 : 85	**–**	–	–	**–**	–

[a] Determined by ^{1}H NMR.

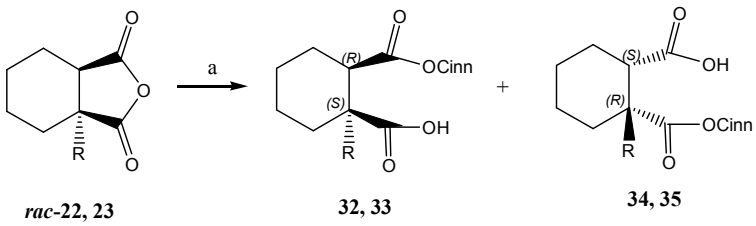
Table 2. Kinetic resolution of anhydrides **11–14** (the stereochemistry of the products is tentatively assigned according to empirical findings)

anhydride	base (mol %)	monoesters	Product ratio[a]	*ee*[b]
rac-**11**	quinine (110)	**24**, **28**	65/35	56/92
rac-**11**	quinidine (110)	ent-**24**, ent-**28**	75/25	52/90
rac-**11**	(DHQD)2AQN (15)	ent-**24**, ent-**28**	45/55	78/32
rac-**11**	(DHQD)2AQN (20)	ent-**24**, ent-**28**	60/40	76/85
rac-**11**	(DHQD)2AQN (30)	ent-**24**, ent-**28**	65/35	70/60
rac-**12**	quinine (110)	**25**, **29**	55/45	56/76
rac-**12**	quinidine (110)	ent-**25**, ent-**29**	60/40	64/78
rac-**12**	(DHQD)2AQN (15)	ent-**25**, ent-**29**	40/60	82/30
rac-**12**	(DHQD)2AQN (20)	ent-**25**, ent-**29**	45/55	75/40
rac-**13**	quinine (110)	**26**, **30**	55/45	55/86
rac-**13**	quinidine (110)	ent-**26**, ent-**30**	55/45	58/82
rac-**13**	(DHQD)2AQN (15)	ent-**26**, ent-**30**	45/55	70/25
rac-**13**	(DHQD)2AQN (20)	ent-**26**, ent-**30**	45/55	78/42
rac-**14**	quinine (110)	**27**, **31**	20/80	76/76
rac-**14**	quinidine (110)	ent-**27**, ent-**31**	15/85	60/92
rac-**14**	(DHQD)2AQN (15)	ent-**27**, ent-**31**	15/85	68/48
rac-**14**	(DHQD)2AQN (20)	ent-**27**, ent-**31**	20/80	76/84

[a] Determined by RP-HPLC at 229 nm.
[b] Determined by chiral HPLC (Chiralpak AS, *n*-hexane/*i*-PrOH/TFA = 96/4/0.1).

acidic workup, was alkylated in the presence of LiHMDS. Subsequently, alkylated lactones **17–19** were oxidized to dicarboxylic acids **20**, **21** and then converted to anhydrides **22** and **23**. Unfortunately, lactone **19**, possessing a benzylic group, did not endure the oxidation and decomposed under the reaction conditions.

Alcoholysis of anhydrides was performed using quinine or quinidine and $(DHQD)_2AQN$ as chiral bases. Those bases have been frequently used for the desymmetrization of variety of anhydrides, hence the direction of opening is highly predictable under the defined reaction conditions.[1d,1e,10] Whereas $(DHQD)_2AQN$ and similar catalysts are readily used in catalytic quantities (up to 30 mol %) natural cinchona alkaloids have to be added in stoichiometric quantity to obtain adequate results. This is explained by the fact that alkaloid-product complex formed during the course of the reaction is still catalytically active, but less enantioselective.[10b] Already, during the preparation of racemic standards for chiral HPLC it was noticed that anhydrides **11–14** were opened only from the less hindered side, regardless of α-substituent, meaning that they are substrates for a kinetic resolution. The reactions were performed in toluene with cinnamyl alcohol as primary nucleophile (Scheme 3.) and the results are summarized in Table 2. To get better insight in the course of the reaction and stereochemical outcome, the residual anhydride was quenched after 40 h with *p*-methoxybenzyl alcohol, which reacts significantly faster than cinnamyl.[3] Prior the analysis, the catalyst and the excess of nucleophiles were removed from the reaction mixtures by acid-base extractions as described earlier.[11] For monoesters **24–27** the best *ee* were achieved with $(DHQD)_2AQN$ as chiral base (68–82 % *ee*), while for



***rac*-22, 23** **32, 33** **34, 35**

Scheme 4. Parallel kinetic resolution of α-alkylated cyclohexane-fused succinic anhydrides. Reagents and conditions: (a) toluene, anhydride (5 mg, *c* = 0.02 mmol/mL), base, cinnamyl alc. (1 eqv.), –30 °C (70 h).

Table 3. Parallel kinetic resolution of anhydrides **22**, **23** (the stereochemistry of the products is tentatively assigned according to empirical findings)

anhydride	base (mol %)	monoesters	Product ratio[a]	*ee*[b]
rac-**22**	quinine (110)	**32**, **34**	84/16	76/89
rac-**22**	quinidine (110)	ent-**32**, ent-**34**	84/16	80/86
rac-**22**	(DHQD)2AQN (15)	ent-**32**, ent-**34**	84/16	87/86
rac-**22**	(DHQD)2AQN (20)	ent-**32**, ent-**34**	85/15	83/82
rac-**23**	quinine (110)	**33**, **35**	53/47	78/39
rac-**23**	quinidine (110)[c]	ent-**33**, ent-**35**	55/45	68/69
rac-**23**	(DHQD)2AQN (15)[c]	ent-**33**, ent-**35**	57/43	79/82
rac-**23**	(DHQD)2AQN(20)[c]	ent-**33**, ent-**35**	62/38	82/67

[a] Determined by RP-HPLC.

[b] Determined by chiral HPLC (Chiralpak AS, *n*-hexane/*i*-PrOH/TFA = 96/4/0.1).

[c] at +4 °C.

monoesters **28**-**31** quinidine gave higher enantioselectivities (76–92 % *ee*) compared to $(DHQD)_2AQN$ (Table 2.). The discrepancy between product ratio and observed enantiomeric excesses, especially in the case of anhydride **14,** is ascribed to the product instability noticed during the workup. This approach facilitates HPLC analysis, nevertheless most of the product mixtures were found hardly separable. Thus, for spectroscopic characterization, small amounts were separated either by column chromatography or by HPLC. Of course, if necessary, each cinnamyl monoester can be obtained in a pure form if addition of the second nucleophile is omitted.

In contrast, but not surprising, less rigid anhydrides **22** and **23** underwent parallel kinetic resolution under the same reaction conditions (Scheme 4., Table 3.). $(DHQD)_2AQN$ as chiral base gave both monoesters in *ee* higher than 80 % while α-substituent had influence on product ratio in monoester mixture. After approximately 70 h of stirring, according to HPLC, the rate of opening considerably slowed down and the reactions were terminated, although the conversion was incomplete. The reaction of anhydride **23** catalyzed by quinidine was too slow at –30 °C, consequently reaction was carried out at +4 °C. Again, product mixture appeared hardly separable; consequently required amounts for spectroscopic characterization were obtained by preparative HPLC.

In conclusion, two series of bicyclic succinic anhydrides alkylated at α-position have been prepared and submitted to alcoholysis in the presence of chiral alkaloid bases. The first series, possessing a cyclopentane ring fused to anhydride moiety opens only from the less hindered side, *i.e.* both enantiomers of > 80 % *ee* can be obtained by kinetic resolution conditions depending on the catalyst used. More flexible cyclohexane fused anhydride undergoes parallel kinetic resolution, both monoesters being produced in over 80 % *ee*.

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