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Highly Selective Hydroformylation of the Cinchona Alkaloids

Marielle Lambers, Felix H. Beijer, José M. Padron, Imre Toth, and Johannes G. de Vries*

DSM Fine Chemicals−Advanced Synthesis & Catalysis, P.O. box 18, 6160 MD Geleen, The Netherlands

Hans-JG.Vries-de@dsm.com

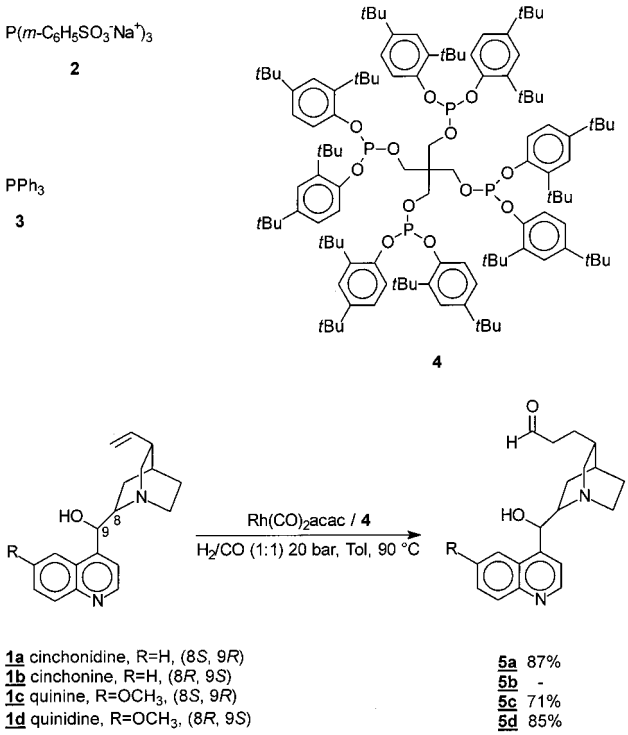
Received January 11, 2002

Abstract: The four naturally occurring cinchona alkaloids were subjected to hydroformylation to create an extra functional group that allows immobilization. Cinchonidine, quinine, and quinidine, could be hydroformylated with virtually complete terminal selectivity, using a rhodium/tetraphosphite catalyst. The cinchonidine aldehyde was reduced to the alcohol and subjected to reductive amination with benzylamine.

The cinchona alkaloids take a central place in the limited reservoir of naturally occurring chiral compounds. Because of their interesting structure and architecture, harboring a unique combination of polar and lipophilic groups, they have found extensive use as catalysts[1] and as chiral host compounds.[2] Further functionalization, particularly at the aliphatic nitrogen and the alcohol function, has created new families of highly enantioselective catalysts.[3−5]

The presence of these two functional groups make the Cinchona alkaloids uniquely suited for a combinatorial approach to catalysis[6] and chiral recognition.[7] Although an obvious strategy for attachment of the alkaloids to a solid support would be to link on either nitrogen or oxygen; this would severely compromise the accessible diversity.[8] For this reason, we have explored methods to convert the double bond that is available in all four naturally occurring cinchona alkaloids into a functional group that can be used as a linker, such as a carboxylic acid or an aldehyde. In our hands, methods described in the literature for the oxidation of the double bond to the aldehyde[9,10] or carboxylic acid[11] either suffered from low yields or led to epimerization at C-3. The latter problem can best be resolved by moving the new carbonyl function further away from the chiral center. Hence, we turned to hydroformylation for the introduction of an aldehyde functionality.[12] As formation of the iso aldehyde introduces another chiral center and thus raises the problem of diastereomers, we required a method that leads to very high terminal selectivity. Fearing that the strong basic function present in the cinchonas might have a detrimental effect on catalyst activity, we first explored the hydroformylation of an aqueous solution of cinchonidine (**1a**), brought to pH 6.0 with 2 N H_2SO_4. Surprisingly, hydroformylation using the water-soluble catalyst $Rh(CO)_2$acac/TPPTS[13] (**2**)[12] at 90 °C and 20 bar CO/H_2 (1:1) led to slow and unselective reactions. Hydroformylation with $Rh(CO)_2$acac/TPP* (**3**)[12] in toluene proceeded much better and gave aldehyde **5a** in 67% yield as a 3:1 mixture of n/iso isomers. Eventually, use of **4** (L/Rh 1.2−1.5), one of the bulky polydentate phosphite ligands that were developed by Mitsubishi Kasei,[14] allowed the highly

SCHEME 1. Hydroformylation of the Cinchona Alkaloids



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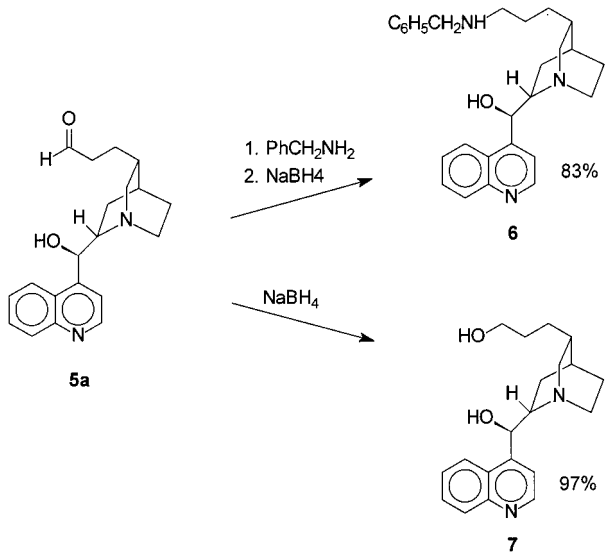
(13) Abbreviations: TPPTS = tris(*m*-sulfonatophenyl)phosphine tris sodium salt, TPP = triphenylphosphine, acac = acetylacetonate.

10.1021/jo0255173 CCC: $22.00
Published on Web 06/13/2002

SCHEME 2



selective hydroformylation of three out of the four naturally occurring cinchona alkaloids (Scheme 1). In fact, the reactions were performed on a slurry of the starting material and gave slurries of pure terminal aldehyde directly, or after concentration of the product solution. The solids thus obtained in good yields did not contain any of the unwanted iso isomers. We have performed all three reactions successfully on a scale of 100 g. The low conversion (40%, product not isolated) of cinchonine (**5b)** may be related to its poor solubility in toluene.

With these three aldehydes in hand, the way is now open to immobilization, for instance, via reductive amination of polymeric amines. The feasibility of this reaction was proven by reductive amination of **5a** with benzylamine via $NaBH_4$ reduction of the preformed imine in ethanol in 83% isolated yield. Direct reduction of **5a** with $NaBH_4$ gave the alcohol in 97% yield (Scheme 2).

The attachment of the Cinchona aldehydes to polymeric amines is currently under study as well as their use in the construction of chiral host libraries.

Experimental Section

General Remarks. Chemicals were purchased from commercial suppliers and used as received. Solvents were of analytical grade and used without further purification. All NMR spectra were recorded in $CDCl_3$.

10,11-Dihydrocinchonidine-11-carbaldehyde 5a. A deoxygenated solution of $Rh(CO)_2acac$ (11.9 mg, 0.0416 mmol) and **4** (98 mg, 0.0516 mmol) in toluene (5 mL) was added via syringe to a slurry of **1a** (5.00 g, 17 mmol) in deoxygenated toluene (20 mL) in a Parr autoclave (125 mL). The reaction mixture was stirred at 90 °C at 20 bar H_2/CO 1:1 v/v pressure for 20 h. After cooling, the white precipitate was filtered off and washed with toluene (2 × 10 mL). Yield: 4.78 g, 87% of **5a**. Mp: 200−201 °C. ^{1}H NMR: δ 9.67(t, 1H, J = 1.5 Hz), 8.72 (d, 1H, J = 4.5 Hz), 8.04 (ABd, 1H, J = 7.8 Hz), 7.92 (ABd, 1H, 8.3 Hz) 7.70−7.15 (m, 3H), 5.62 (d, 1H, J = 3.0 Hz), 5.30 (s, 1H), 3.60−3.40 (m, 1H), 3.10−2.85 (m, 2H), 2.75−2.40 (m, 2H), 2.40−2.15 (m, 3H), 1.90−1.60 (m, 4H), 1.60−1.25 (m, 4H) ppm. ^{13}C NMR: δ 202.1, 150.0, 149.7, 148.0, 130.1, 129.0, 126.6, 125.6, 122.9, 118.2, 71.7, 60.1, 58.2, 43.1, 41.8, 34.9, 28.0, 26.7, 25.7, 20.9 ppm. IR: ν 3066, 2927, 2860, 2709, 1724 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.0; H, 7.5; N, 8.6. Found: C, 74.2; H, 7.4; N, 8.7.

10,11-Dihydroquinine-11-carbaldehyde 5c. A similar procedure was used for the preparation of compound **5c** with the following alterations: hydroformylation of quinine **1c** (1.0192 g, 3.14 mmol), $Rh(CO)_2acac$ (8.9 mg, 0.0379 mmol), and **4** (96.5 mg, 0.0509 mmol) resulted in a clear solution. After partial concentration under reduced pressure and cooling of the resulting solution, aldehyde **5c** (790.7 mg, 71%) crystallized as a white solid. Mp: 104−107 °C. ^{1}H NMR: δ 9.70 (t, 1H, J = 1.5 Hz), 8.55 (d, 1H, J = 4.4 Hz), 7.93 (ABd, 1H, J = 8.9 Hz), 7.46 (d, 1H, 4.9 Hz), 7.35−7.10 (m, 2H), 5.49 (d, 1H, J = 3.9 Hz), 4.25 (bs, 1H), 3.89 (s, 3H), 3.55−3.30 (m, 1H), 3.15−2.85 (m, 2H), 2.70−2.50 (m, 1H), 2.45−2.20 (m, 4H), 1.85−1.25 (m, 7H) ppm. ^{13}C NMR: δ 202.1, 157.7, 147.8, 147.5, 144.2, 131.5, 126.6, 121.4, 118.4, 101.4, 72.0, 59.8, 58.3, 55.7, 43.1, 41.9, 35.1, 28.1, 26.8, 25.6, 21.3 ppm. IR: ν 3600−2500, 3074, 2930, 2860, 2714, 1720 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.2; H, 7.4; N, 7.9. Found: C, 70.9; H, 7.3; N, 7.6.

10,11-Dihydroquinidine-11-carbaldehyde 5d. A similar procedure was used for the preparation of compound **5d** with the following alterations: hydroformylation of quinine **1d** (1.0039 g, 3.09 mmol), $Rh(CO)_2acac$ (11.2 mg, 0. 0433 mmol), and **4** (97.4 mg, 0.0514 mmol) resulted in a clear solution. After partial concentration under reduced pressure and cooling of the resulting solution, aldehyde **5d** (933.9 mg, 85%) crystallized as a white solid. Mp: 110−112 °C. ^{1}H NMR: δ 9.77 (s, 1H), 8.57 (d, 1H, J = 4.4 Hz), 7.93 (ABd, 1H, J = 8.9 Hz), 7.52 (d, 1H, J = 4.4 Hz), 7.35−7.10 (m, 2H), 5.63 (bs, 1H), 5.12 (bs, 1H), 3.82 (s, 3H), 3.30−3.10 (m, 1H), 3.10−2.55 (m, 4H), 2.50−2.30 (m, 1H), 2.15−1.10 (m, 9H) ppm. ^{13}C NMR: δ 202.5, 157.7, 148.0, 147.5, 144.0, 131.4, 126.5, 121.5, 118.4, 101.2, 71.8, 59.6, 55.6, 50.9, 50.1, 42.0, 35.1, 27.0, 26.4, 24.5, 20.3 ppm. IR: ν 3500−2500, 2935, 2868, 1721 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.2; H, 7.4; N, 7.9. Found: C, 71.1; H, 7.4; N, 7.6.

11-*N*-Benzylaminomethyl-10,11-dihydrocinchonidine 6. A suspension of aldehyde **5a** (498.9 mg, 1.54 mmol) and benzylamine (173.9 mg, 1.62 mmol) in toluene (50 mL) was heated under reflux, while H_2O was azeotropically distilled off. After 3 h, the resulting clear and colorless reaction mixture was cooled, resulting in the partial precipitation of the product. The toluene was removed in vacuo affording the imine (625.1 mg, 98%) as a white solid. ^{1}H NMR: δ 8.78 (d, 1H, J = 4.5 Hz), 8.07 (ABd, 1H, J = 8.3 Hz), 7.93 (ABd, 1H, J = 8.4 Hz), 7.70−7.15 (m, 9H), 5.61 (bs, 1H), 4.82 (bs, 1H), 4.48 (s, 2H), 3.55−3.35 (m, 1H), 3.15−2.90 (m, 2H), 2.70−2.05 (m, 4H), 1.85−1.20 (m, 8H) ppm.

Sodium borohydride (60.2 mg, 1.59 mmol) was added portionwise to a solution of the crude imine in EtOH (20 mL). The mixture was stirred for 3 h at ambient temperature. Quenching with H_2O (20 mL) resulted in the precipitation of a white solid. The mixture was extracted with chloroform (3 × 50 mL). The precipitate dissolved in the organic phase. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness, giving amine **6** (519.7 mg, 83%) as a white solid. Mp: 128−131 °C. ^{1}H NMR: δ 8.71 (d, 1H, J = 4.4 Hz), 8.04 (ABd, 1H, J = 7.9 Hz), 7.90 (ABd, 1H, J = 8.4 Hz), 7.65−7.45 (m, 2H), 7.30−7.05 (m, 6H), 6.43 (bs, 1H), 5.62 (s, 1H), 3.65 (s, 2H), 3.60−3.40 (m, 1H), 3.05−2.80 (m, 2H), 2.65−2.10 (m, 4H), 1.90−1.05 (m, 11 H) ppm. ^{13}C NMR: δ 150.3, 150.0, 148.0, 140.1, 130.1, 128.9, 128.3, 128.1, 126.9, 126.5, 125.6, 123.0, 118.3, 71.4, 60.1, 58.6, 54.0, 49.4, 43.2, 35.4, 32.4, 28.1, 27.9, 25.8, 20.7 ppm. IR: ν 3500−2500, 3063, 2926, 2860 cm^{-1}. HRMS (EI): calcd for $C_{27}H_{33}N_3O$ 415.2624, found 415.2619.

11-Hydroxymethyl-10,11-dihydrocinchonidine 7. Sodium borohydride (60.2 mg, 1.59 mmol) was added portionwise to a solution of aldehyde **5a** (482.4 mg, 1.49 mmol) in EtOH (10 mL). The mixture was stirred for 4 h at ambient temperature. The reaction was quenched with H_2O (20 mL), and the resulting suspension was extracted with chloroform (3 × 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent under reduced pressure, alcohol **7**

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(470.5 mg, 97%) was obtained as a white solid. Mp: 104−107 °C. ^{1}H NMR: δ 8.67 (d, 1H, J = 4.4 Hz), 8.02 (ABd, 1H, J = 8.4 Hz), 7.91 (ABd, 1H, J = 8.4 Hz), 7.65−7.45 (m, 2H), 7.40−7.20 (m, 1H), 5.80−5.40 (m, 2H), 3.65−3.40 (m, 3H), 3.23 (bs, 1H), 3.10−2.85 (m, 2H), 2.70−2.35 (m, 2H), 2.35−2.15 (m, 1H), 1.85−1.10 (m, 9H) ppm. ^{13}C NMR: δ 149.9, 147.9, 129.9, 129.0, 126.6, 125.6. 123.0, 118.3, 71.5, 62.5, 60.1, 58.6, 43.2, 35.3, 31.0, 30.7, 28.1, 25.9, 21.0 ppm. IR: ν 3500−3000, 2927, 2862 cm^{-1}. HRMS (EI): calcd for $C_{20}H_{26}N_2O_2$ 326.1994, found 326.2004.

Acknowledgment. This work was carried out as part of a European TMR-network Chiral Separations ERB FMRX-CT-98-233.

Supporting Information Available: ^{1}H and ^{13}C NMR of compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0255173