Synthesis of quinine and quinidine using sulfur ylide-mediated asymmetric epoxidation as a key step

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ABSTRACT

The epoxidation of meroquinene aldehyde with a chiral sulfur ylide as the key step in the synthesis of quinine and quinidine is described. The epoxidation reactions proceed under reagent control with high selectivity and good yield. The effect of sulfide and ylide substituents on the stereochemical outcome of the reaction is discussed.

1. Introduction

Asymmetric sulfur ylide methodology provides a complementary route to epoxides but, perhaps more importantly, it offers a different disconnection to alkene oxidation.1 The optimum ylide substrates are those derived from semi-stabilized ylides (aryl or alkenyl) since they often react with aromatic and aliphatic aldehydes with good levels of diastereo- and enantiocontrol when appropriate chiral sulfides are employed. The most important carbonyl electrophiles are aliphatic or alkenyl aldehydes rather than aromatic aldehydes as these lead to the more synthetically useful arylalkyl or alkenylalkyl epoxides.2 Over recent years we have described two chiral sulfides 1 and 2 that deliver high enantio- and good diastereoselectivity with aliphatic aldehydes (Scheme 1).3,4 For example, sulfide 1, available in five steps from camphor sulfonic acid,5 gave 90:10 dr and 99:1 er in the reaction of the corresponding benzyl sulfonium salt with valeraldehyde.6 Sulfide 2, available in one step from limonene, gave 91:9 dr and 99:1 er.3a The high selectivities achieved prompted us to test this methodology in the synthesis of complex molecules.7

Herein, we describe the application of chiral sulfur ylide epoxidations to the synthesis of quinine, a molecule with a long and venerable history, spanning folklore, medicine, synthesis, and catalysis and not without controversy as well.8 Our retrosynthetic analysis (Scheme 2) led us back to epoxide 3, a strategy which had been previously used by Uskokovic, Jacobsen, and Kobayashi.9 Jacobsen and Kobayashi were able to control the stereochemistry of the epoxide through Sharpless dihydroxylation of the corresponding trans-alkene. However, the epoxide can also be disconnected back to sulfonium salt 4 and meroquinene aldehyde 5 leading to a more convergent synthesis. Sulfonium salts like 4 bearing nucleophilic nitrogen atoms are unstable and so protection of the nitrogen was required.

We have previously described the protection of the amino group as a carbamate moiety—using sulfide 2 gave the sulfonium salt 4 as the key intermediate. To achieve this, the sulfone 7 was protected as the TEOs ether 6 and then converted to the sulfonium salt 4 via the corresponding sulfenate. The sulfenate 6 was obtained from the corresponding sulfide 2 following the derived conditions.

In this paper, we describe the epoxidation of meroquinene aldehyde 5 with chiral sulfur ylides to deliver the key epoxide 3, which was then converted to quinine and quinidine. The epoxidation reactions proceed under reagent control with high selectivity and good yield. The effect of sulfide and ylide substituents on the stereochemical outcome of the reaction is discussed.
salt 6. In the key step, epoxidation of meroquinene aldehyde 5 with the ylide derived from 6 gave a mixture of trans/cis epoxides (89:11) with complete control over relative stereochemistry (i.e., only one of the two possible trans-epoxides was formed; Scheme 3).1a

We were interested in alternative protecting groups and expected that by keeping the quinoline ring intact, higher trans/cis selectivity might be achieved. We therefore focused on the 2-bromoquinolyl sulfonium salt 7. We hypothesized that the bromo-substituent would hinder the quinoline nitrogen and thereby reduce its nucleophilicity. We elected to test both sulfides 1 and 2 in this strategy.

2. Results and discussion

Scheme 4 shows the synthesis of the required sulfonium salts. Reaction of acetyl acetamide 8 with Br₂ in CHCl₃ gave the bromo derivative 9 in 98% yield.10 Subsequent cyclication of 9 with 49% H₂SO₄ followed by bromination using POBr₃ gave dibromide 10 in 75% yield over two steps.11 Reaction of the dibromide 10 with sulfides 1 and 2 afforded the corresponding sulfonium salts 11 and 12. However, whilst sulfonium salt 11 was indefinitely stable, salt 12 began to decompose to sulfide 13 in solution over a short period of time (Scheme 5). A brief investigation revealed that the source of instability was not the nature of the 2-substituent since sulfonium salts bearing H or SiMe₃ decomposed in a similar manner. In contrast, the 1-naphthyl sulfonium salt 15 prepared from 1-(bromomethyl) naphthalene 14 was stable, thus it seems that the quinoline nitrogen was primarily responsible for the instability of sulfonium salt 12 (Scheme 5). We therefore progressed with the stable sulfonium salt 11.

Treatment of the salt 11 with KOH in the presence of meroquinene aldehyde 516 gave the required epoxide 16 with perfect trans selectivity and as a 93:7 mixture of the two trans-diastereomers 16 and 18 (Scheme 8).

The high trans/cis selectivity and diastereoselectivity can be accounted for by considering the fate of the betaine intermediates (Scheme 6).13 The trans/cis selectivity is determined by the extent of reversibility in the formation of syn-betaines 19A. In the case of unhindered aliphatic aldehydes the extent of reversibility is usually only partial, leading to only moderate trans/cis selectivity. The very high trans-selectivity observed here most likely arises because the ylide is especially stable (the negative charge can be delocalized onto the amine nitrogen) and so syn-betaine formation becomes fully reversible. Under such Curtin-Hammett conditions the reaction funnels through the betaine with the lower barrier to epoxide formation which delivers the trans-epoxide with high selectivity.

Diastereomers 16 and 18 arise from the fact that the steps for the formation of two diastereomeric anti-betaines (which lead to the trans epoxides) are also reversible but not to the same extent. Dissociation of anti-betaine C (which would give the minor diastereomer of the epoxide) to ylide conformer B is less favored since it leads to a more hindered (and therefore less stable) ylide conformer. Thus, even though the more hindered ylide conformer B is likely to be present in much smaller amounts than A, the reduced tendency for its corresponding betaine C to revert back to starting materials results in an ‘over-expression’ of this pathway and so lower the dr (Scheme 7).
The diastereoselectivity was dependent on the reaction conditions and increased with increasing amounts of t-BuOH (83:17 with MeCN:t-BuOH, 15:1, versus 93:7 with MeCN:t-BuOH, 1:5). Protic solvents are known to assist the bond rotation step and thereby reduce the extent of reversibility in betaine formation. Interestingly, in the reaction of the ylide derived from 11 with merocaraldehyde 5 we needed to minimise reversibility in betaine formation (by using a high concentration of protic solvent) to maximise the diastereoselectivity of the reaction (perfect trans:cis selectivity was observed) whilst with the ylide derived from 6 we needed to maximise reversibility in betaine formation (by using a low concentration of protic solvent) to maximise the trans:cis selectivity of the reaction (perfect diastereoselectivity was observed).

The dr is thus determined by the degrees of reversibility in the formation of the two diastereomeric anti-betaines. Had there been essentially no reversibility in formation of the anti-betaines, the selectivity of trans-epoxide would have been higher still. Interestingly, if sulfonium salt 12 had been stable enough to use, we now predict that it would have given lower selectivity for the desired trans-epoxide since sulfide 2 is more hindered and so would have led to a greater degree of reversibility in anti-betaine formation. Based on structure, the extent of betaine reversibility is dependent on the bulk of the sulfide and the stabilization of the ylide afforded by the ylide substituent.

The synthesis of quinine was completed by CsF-mediated deprotection/cyclization in DMF/t-BuOH (9:1) followed by Zn/AcOH reduction of the C–Br bond to furnish the target quinine in 73% yield over two steps and the corresponding epoxide 16 (Scheme 8).

Reaction of the opposite enantiomer of the sulfide 1 with dibromide 10 gave the sulfonium salt 17, which on epoxidation with merocaraldehyde 5 led to preferential formation of the other diastereoisomer of epoxide 18 and with similar diastereoselectivity (89:11 dr, complete trans selectivity) (Scheme 8). This shows that the selectivity in the epoxidation reaction is dominated by the stereochemistry of the sulfide (reagent control); the existing stereochemistry of the merocaraldehyde 5 does not influence the outcome of reaction. The synthesis of quinidine was completed by CsF-mediated deprotection/cyclization in DMF/t-BuOH (9:1) followed by Zn/AcOH reduction of the C–Br bond to furnish the target quinidine in 72% yield over two steps from the corresponding epoxide 18.

3. Conclusions

In conclusion, we have described the use of a chiral sulfur ylide in the epoxidation of merocaraldehyde as the key step in the synthesis of quinine and quinidine. In the course of our studies we discovered an unexpected instability issue surrounding the quinolyl sulfonium salt derived from the hindered sulfide 2, which has an inherent tendency to undergo base-promoted elimination. The less hindered sulfide 1 gave a much more stable quinolyl sulfonium salt, which reacted with merocaraldehyde 5 with high trans selectivity (>95:5) and high diastereoselectivity (93:7) for the desired trans-epoxide. Despite the subtle factors governing selectivity, no matched/mis-matched issues arose since the opposite sulfide enantiomer gave essentially the same high trans selectivity (>95:5) and diastereoselectivity (89:11) but now in favor of the other trans stereoisomer. This study highlights how subtle effects in the structure of the sulfide and the ylide substituent can affect the stereocchemical outcome of epoxidations with aliphatic aldehydes.

4. Experimental

4.1. 4-Bromo-N(4-methoxyphenyl)-3-oxobutanamide 9

A solution of bromine (6.2 ml, 0.12 mol) in CHCl₃ (60 ml) was added dropwise (over a period of 2.5 h) to a 0 °C cooled stirred solution of p-acetoaceticacid 8 (25.0 g, 121 mmol) in CHCl₃.
(120 ml) under a nitrogen atmosphere. After complete addition, the reaction mixture was stirred at rt for 18 h. Additional CHCl3 (50 ml) was then added and air was bubbled through the reaction mixture for 2 h. The reaction mixture was filtered and the solid residue was washed with a mixture of acetone/pet. ether (1:4) to get a colorless solid, which was recrystallized from methanol to afford ketobromide 9 (33.84 g, 98%) as colorless needles. Mp 133–135°C (MeOH), lit. 15 mp 131–134°C (EtOH); Rf (EtOAc/pet. ether, 2:3) 0.45; 2H, s, CH2Br, 3.95 (2H, s, CH2), 3.76 (3H, s, OCH3); δC (100 MHz, CDCl3) 161.5 (4C), 144.5 (4C), 137.6 (4C), 135.1 (4C), 131.0 (CH), 127.5 (4C), 125.9 (4C), 124.6 (CH), 100.5 (CH), 70.5 (CH), 60.0 (4C), 45.2 (CH), 44.0 (CH2), 43.6 (CH), 42.7 (CH2), 31.6 (CH2), 26.7 (2H), 26.5 (CH2), 24.5 (CH2), 21.9 (CH2), 19.0 (CH3); m/z (ESI+) 500 [M–BF4]+, 502 [M+2–BF4]+, 284, 286, 250 [M–BF4–C3H7OS]+, 252 [M+2–BF4–C3H7OS]+; HRMS (ESI+) C26H31BrNO5 (M+) requires: 500.1253; found: 500.1236.

4.3. (R,3S)-2-((Trimethylsilyl)ethyl) 4-(((2-Bromo-6-methoxyquinolin-4-yl)oxiran-2-yl)methyl)-3-vinylpiperidine-1-carboxylic acid 16

Manually ground KOH (28.6 mg, 0.511 mmol) was added to a solution of sulfonate salt 11 (100 mg, 0.170 mmol) in CH3CN/t-BuOH (1:5) (0.6 ml, 0.3 M) containing merocoumarin aldehyde 6 (101 mg, 0.340 mmol) at 0°C under an argon atmosphere. The resulting turbid yellow solution was stirred at 0°C for 48 h. CH3CN was evaporated under vacuum and water (10 ml) was added and the aq layer was extracted with EtOAc (4 x 10 ml). The combined organic layers were washed with brine, dried over MgSO4, and concentrated under reduced pressure. The crude material (dr 93:7 trans:trans) was purified by flash silica gel column chromatography (EtO/ pentane 1:2) to afford a mixture of the two trans epoxides 16 and 18 (94:6, 69 mg, 74%) as a light yellow gum; Rf (EtO/ pentane 1:1) 0.30; 16: δ3 (400 MHz; acetone-d6) 7.90 (1H, d, J = 9.3 Hz, ArH), 7.53 (1H, d, J = 2.7 Hz, ArH), 7.47 (1H, dd, J = 9.3, 2.7 Hz, ArH), 7.36 (1H, d, J = 0.5 Hz, ArH), 5.92 (1H, dd, J = 17.3, 10.5, 8.8 Hz, CH=CHH), 5.18 (1H, ddd, J = 17.3, 2.1, 1.1 Hz, CH=CH), 5.13 (1H, dd, J = 10.5, 2.1 Hz, CH=CHH), 4.45 (1H, dd, J = 2.0, 0.5 Hz, OCH–Ar), 4.11–4.17 (3H, m, Me3Si–CH2–CH2O and CHHNN), 4.02–4.10 (1H, m, CHHNN), 3.98 (3H, s, OCH3), 3.15 (1H, ddd, J = 7.2, 4.0, 2.0 Hz, CH3–OCH), 2.87–3.04 (1H, m, CHHNN), 2.45–2.48 (1H, m, CHHNN), 2.10–2.16 (1H, m, ring CH), 2.00 (1H, ddd, J = 14.3, 6.5, 4.0 Hz, CHO–CH=CHH), 1.51–1.72 (4H, m, CH=OCH=CH–CH=CH2), 0.96–1.02 (2H, m, MeSi–CH2–CH=O), 0.05 (9H, s, SiMe3); δC (100 MHz; acetone-d6) 159.4 (4C), 156.1 (1N(O)=O), 147.0 (4C), 145.0 (4C), 139.6 (4C), 137.1 (CH), 131.3 (CH), 127.5 (4C), 123.6 (CH), 121.5 (CH), 117.6 (CH2), 102.8 (CH3), 83.2 (CH2), 62.8 (CH), 56.3 (CH3), 55.8 (CH), 49.0 (CH2), 44.2 (CH2), 43.5 (CH), 38.9 (CH), 36.3 (CH2), 28.8 (CH2), 18.4 (CH2), –1.3 (CH3 × 3).
4.6. Quinine

CsF (160 mg, 1.05 mmol) was added to a solution of epoxides 16/18 (4:1 trans/trans, 115 mg, 0.211 mmol) in DMF/t-BuOH (9:1, 1.5 ml) and the mixture was heated at 110 °C for 12 h. The reaction mixture was diluted with water (10 ml), basified with aq NaOH (6 M), and extracted with EtOAc (4 × 10 ml). The combined organic layers were washed with water (4 × 20 ml), dried over MgSO4, filtered, and concentrated under reduced pressure. The crude material was dissolved in a mixture of glacial acetic acid/water (9:1, 3 ml). Granulated Zn (20 mesh, 27.5 mg, 0.42 mmol) was added and the resulting mixture was heated at 70 °C for 5 h, diluted with water (10 ml), basified with aq NH3, and extracted with EtOAc (4 × 10 ml). The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (CH2Cl2/MeOH 20:1 containing 0.75% Et3N) to afford a mixture of quinine and quindine (4:1, 50 mg, 73%) as a colorless solid, with spectroscopic data (1H NMR, 13C NMR) matching the reported data.12

4.7. (15S,3S,4R)-2-[(2-Bromo-6-methoxyquinolin-4-yl)-methyl]-3-[(1R,4S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate 17

Sulfide ent-1 (1.50 g, 6.00 mmol) was added to a solution of dibromide 10 (0.993 g, 3.00 mmol) in CH2Cl2 (6.0 ml) followed by the addition of a solution of NaBF4 (1.237 g, 15.0 mmol) in water (3.0 ml, 5 M) and the resulting mixture was heated at 45 °C for 96 h. Water (20 ml) was added and the aq layer was extracted with CH2Cl2 (3 × 20 ml). The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated in vacuum. The crude material was subjected to flash silica gel column chromatography (eluting with CH2Cl2 and then with MeOH/CH2Cl2 20:1) as a light yellow foam; Rf (CH2Cl2/MeOH, 9:1) 0.31; νmax (CHCl3, neat) cm−1: 2964, 1735 (C=O), 124.6 (CH), 100.5 (CH), 70.5 (CH), 60.0 (4C), 59.5 (CH), 56.3 (CH), 43.9 (CH), 37.6 (CH), 36.5 (CH2), 28.3 (CH2), 18.4 (CH2), –1.2 (CH2 × 3).

4.9. Quinidine

CsF (111 mg, 0.731 mmol) was added to a solution of epoxides 18/16 (4:2 trans/trans, 80.0 mg, 0.146 mmol) in DMF/t-BuOH (9:1, 1.10 ml) and the mixture was heated at 110 °C for 12 h. The reaction mixture was diluted with water (10 ml), basified with aq NaOH (6 M), and extracted with EtOAC (4 × 10 ml). The combined organic layers were washed with water (4 × 20 ml), dried over MgSO4, filtered, and concentrated under reduced pressure. The crude material was dissolved in a mixture of glacial acetic acid/water (9:1, 2 ml). Granulated Zn (20 mesh, 19.1 mg, 0.292 mmol) was added and the resulting mixture was heated at 70 °C for 5 h. The reaction mixture was diluted with water (10 ml), basified by aq NH3, and extracted with CH2Cl2 (3 × 20 ml). The combined organic layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (CH2Cl2/MeOH 20:1 containing 0.75% Et3N) to afford a mixture of quinidine and quinidine (4:2:1, 34 mg, 72%) as colorless solid, with spectroscopic data (1H NMR, 13C NMR) matching the reported data.

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References


12. Although aldehyde 5 has been prepared by total synthesis (Ref. 9d), we obtained it directly from commercially available quinine (five steps, Ref. 3a) using following procedures from: Martinelli, M. J.; Paterson, B. C.; Khau, V. V.; Hutchinson, D. R.; Sullivan, K. A. *Tetrahedron Lett.* 1993, 34, 5413; Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* 2001, 42, 3235. Many syntheses of quinine adopt this strategy, that is, are relay syntheses.


