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

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Dedicated to Henri Kagan on the occasion of his 80th birthday

ABSTRACT

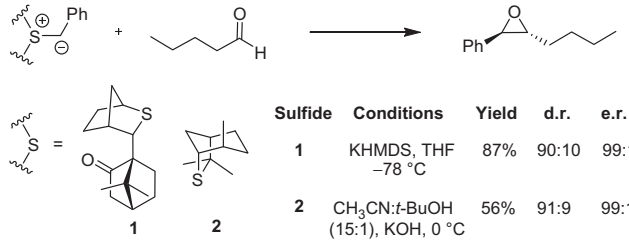
The epoxidation of meroquinene aldehyde with a chiral sulfur ylide as the key step in the synthesis of quinine and quinidine is described. The epoxidation reactions proceed under reagent control with high selectivity and good yield. The effect of sulfide and ylide substituents on the stereochemical outcome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

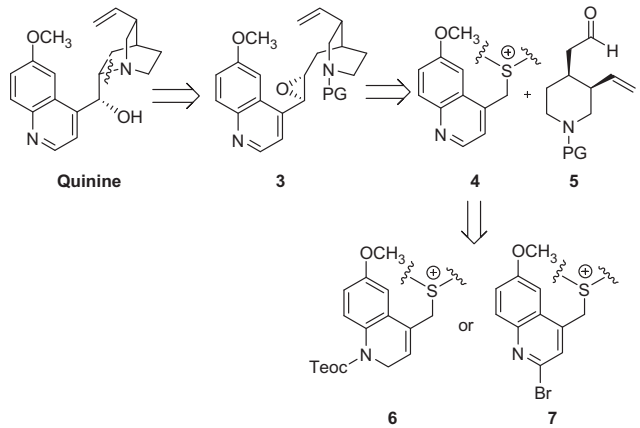
Herein, we describe the application of chiral sulfur ylide epoxidations to the synthesis of quinine, a molecule with a long and venerable history, spanning folklore, medicine, synthesis, and catalysis and not without controversy as well.[8] Our retrosynthetic analysis (Scheme 2) led us back to epoxide **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



Sulfide	Conditions	Yield	d.r.	e.r.
1	KHMDS, THF –78 °C	87%	90:10	99:1
2	CH_3CN:*t*-BuOH (15:1), KOH, 0 °C	56%	91:9	99:1

Scheme 1. Epoxidation of valeraldehyde with sulfides **1** and **2**.



Scheme 2. Retrosynthesis of quinine.

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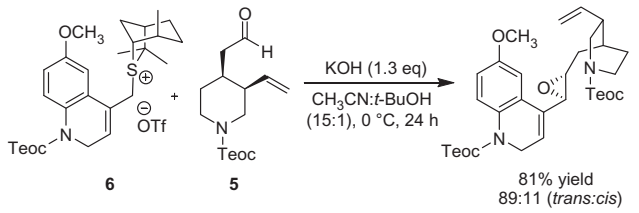
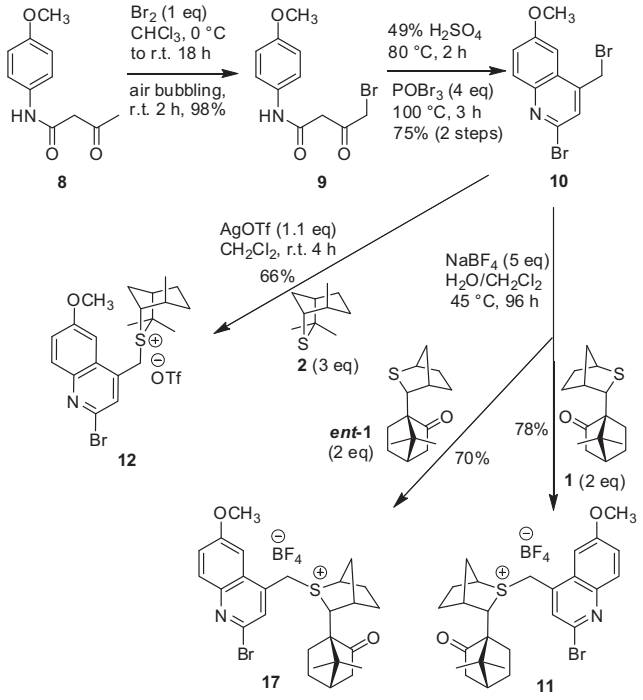
salt **6**. In the key step, epoxidation of meroquinene aldehyde **5** with the ylide derived from **6** gave a mixture of *trans*/*cis* epoxides (89:11) with complete control over relative stereochemistry (i.e., only one of the two possible *trans*-epoxides was formed; Scheme 3).[3a]

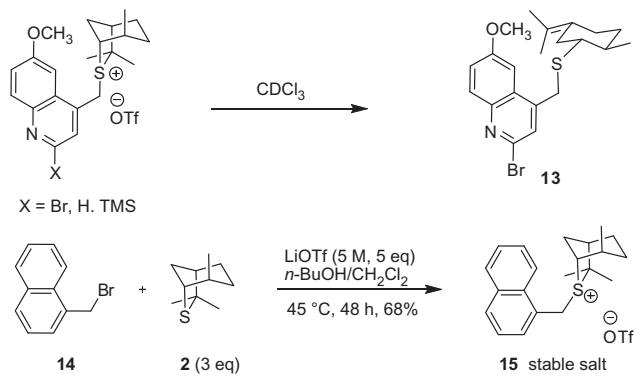
We were interested in alternative protecting groups and expected that by keeping the quinoline ring intact, higher *trans*/*cis* selectivity might be achieved. We therefore focused on the 2-bromo quinolyl sulfonium salt **7**. We hypothesized that the bromo-substituent would hinder the quinoline nitrogen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



Scheme 3. Epoxidation of meroquinene aldehyde **5** using sulfide **2**.



Scheme 4. Synthesis of sulfonium salts **11**, **12**, and **17**.



Scheme 5. Comparison of the stability of sulfonium salts.

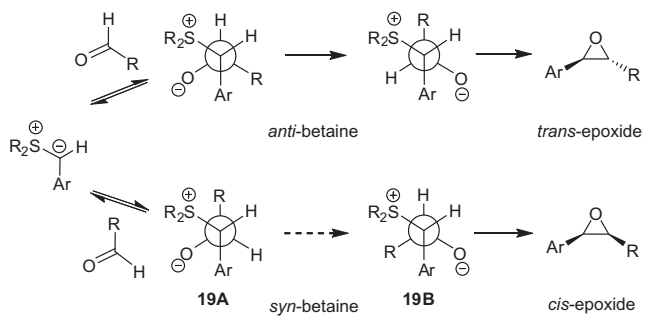
2. Results and discussion

Scheme 4 shows the synthesis of the required sulfonium salts. Reaction of acetyl acetamide **8** with Br_2 in $CHCl_3$ gave the bromo derivative **9** in 98% yield.[10] Subsequent cyclization of **9** with 49% H_2SO_4 followed by bromination using $POBr_3$ 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 $SiMe_3$ 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**.

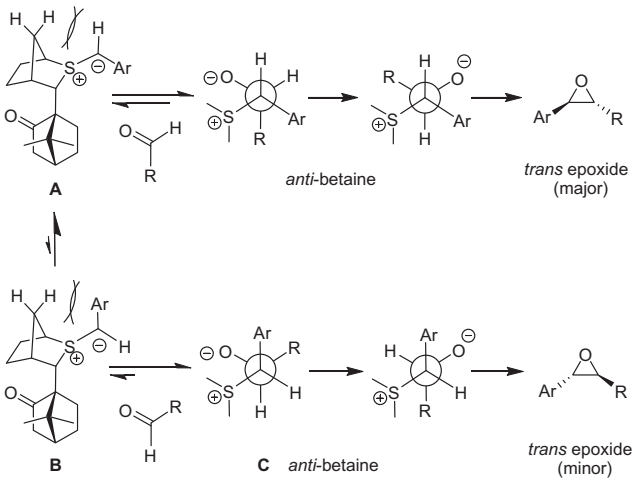
Treatment of the salt **11** with KOH in the presence of meroquinene aldehyde **5**[12] gave the required epoxide **16** with perfect *trans* selectivity and as a 93:7 mixture of the two *trans*-diastereomers **16** and **18** (Scheme 8).

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*-betaine **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).



Scheme 6. Rationalisation of *trans*:*cis* selectivity.



Scheme 7. Effect of reversibility in *anti*-betaine formation on diastereoselective formation of *trans*-epoxides.

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 meroquinene aldehyde **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[9d] in DMF/*t*-BuOH (9:1) followed by Zn/AcOH reduction[11a] of the C–Br bond to furnish the target quinine in 73% yield over two steps from 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 meroquinene aldehyde **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 meroquinene aldehyde **5** does not influence the outcome of reaction. The synthesis of quinidine was completed by CsF-mediated deprotection/cyclization[9d] in DMF/*t*-BuOH (9:1) followed by Zn/AcOH reduction[11a] of the C–Br bond to furnish the target quinidine in 72% yield over two steps from the corresponding epoxide **18**.

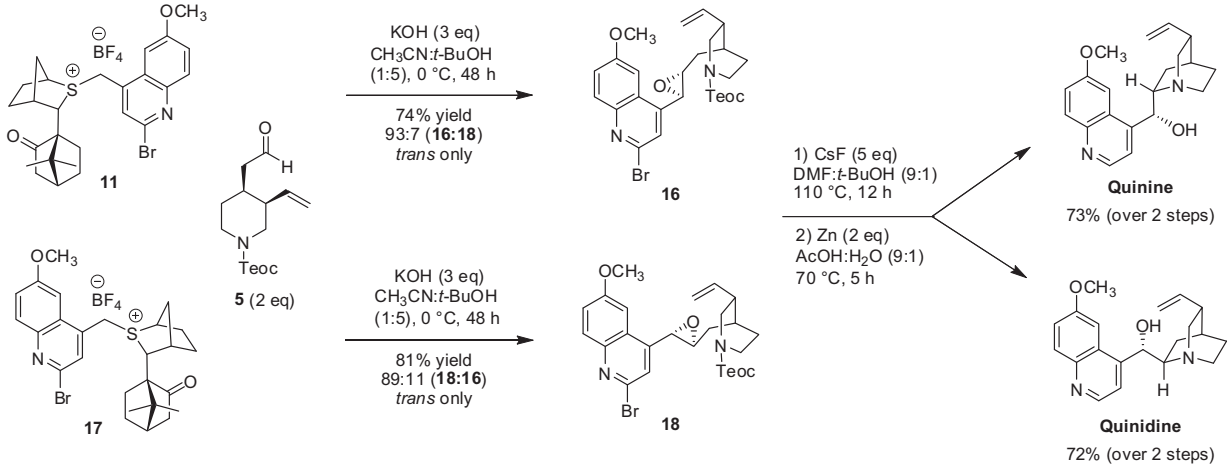
3. Conclusions

In conclusion, we have described the use of a chiral sulfur ylide in the epoxidation of meroquinene aldehyde 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 meroquinene aldehyde **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 stereochemical outcome of epoxidations with aliphatic aldehydes.[14]

4. Experimental

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

A solution of bromine (6.2 ml, 0.12 mol) in $CHCl_3$ (60 ml) was added dropwise (over a period of 2.5 h) to a 0 °C cooled stirred solution of *p*-acetoacetanisidide **8** (25.0 g, 121 mmol) in $CHCl_3$



Scheme 8. The synthesis of quinine and quinidine.

(120 ml) under a nitrogen atmosphere. After complete addition, the reaction mixture was stirred at rt for 18 h. Additional $CHCl_3$ (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); R_f (EtOAc/pet. ether, 2:3) 0.45; ν_{max} ($CHCl_3$, neat)/cm^{-1} 3297 (N–H), 3011, 2938 (C–H), 1729 (C=O), 1648 (NHC=O), 1602, 1546, 1510, 1027; δ_H (400 MHz, CD_3OD) 7.47–7.39 (2H, m, ArH), 6.90–6.85 (2H, m, ArH), 4.28 (2H, s, CH_2Br), 3.95 (2H, s, CH_2), 3.76 (3H, s, OCH_3); δ_C (100 MHz, CD_3OD) 196.5 (C=O), 167.2 (HNC=O), 156.8 (4C), 131.1 (4C), 121.7 (CH × 2), 113.6 (CH × 2), 54.5 (OCH_3), 34.5 (CH_2), 28.9 (CH_2); *m/z* (CI^+) 286 [M+H, $^{79}Br]^+$ (100%), 288 [M+H+2, $^{81}Br]^+$ (98%), 206 $[M+H]^+-Br$; HRMS (CI^+) $C_{11}H_{13}BrNO_3$ (MH^+) requires: 286.0078; found: 286.0079.

4.2. 4-(Bromomethyl)-6-methoxyquinolin-2(1*H*)-one[16]

A solution of ketobromide **9** (0.285 g, 1.0 mmol) and 49% H_2SO_4 (prepared by adding 5 ml of concd H_2SO_4 (98%) to 5 ml of distilled water) was heated at 80 °C for 2 h. The reaction mixture was cooled to rt and poured onto crushed ice. The yellow precipitate generated was filtered with suction, and then washed with cold water, saturated aq $NaHCO_3$ and again with cold water. The solid product was dried in air for 15 h and in vacuum over P_2O_5 for 6 h. The resulting yellow solid was recrystallized using a mixture of EtOH/H_2O (1:1) to afford 2-quinolone as yellow wafers (0.235 g, 88%); mp dec. > 280 °C; ν_{max} ($CHCl_3$, neat)/cm^{-1} 2993, 2825, 1663 (NHC=O), 1622, 1503, 1199, 1037; δ_H (400 MHz, DMSO-d_6) 11.75 (1H, br s, NH) 7.33–7.28 (2H, m, ArH), 7.21 (1H, dd, *J* = 9.0, 3.0, ArH), 6.74 (1H, s, ArH), 4.93 (2H, s, CH_2Br), 3.82 (3H, s, OCH_3); δ_C (100 MHz, DMSO-d_6) 161.5 (HNC=O), 154.6 (4C), 146.9 (4C), 134.2 (4C), 123.1 (CH), 120.1 (CH), 118.3 (4C), 117.6 (CH), 107.6 (CH), 56.1 (OCH_3), 30.5 (CH_2).

4.3. 2-Bromo-4-(bromomethyl)-6-methoxyquinoline 10

$POBr_3$ (22.94 g, 80.0 mmol) was powdered in a mortar and pestle and then mixed with 2-quinolone (5.36 g, 20.0 mmol). This mixture was transferred into an RB flask fitted with a condenser. The system was evacuated and flushed with nitrogen; the reaction mixture was heated at 100 °C for 3 h under a nitrogen atmosphere ensuring that the two solids were well mixed. After cooling to rt, hot water was added very slowly and cautiously, and then the mixture was poured onto crushed ice. The resulting pale yellow precipitate was filtered with suction and washed with water. The precipitate was dissolved in CH_2Cl_2, dried over $MgSO_4$, and filtered. Decolorizing charcoal was added to the filtrate and stirred for 1 h. The charcoal was removed by filtration and the filtrate was evaporated under reduced pressure to give a pale yellow solid, which was purified by passing though a short silica plug and eluting with CH_2Cl_2 to afford *dibromide* **10** (5.65 g, 85%, 90% br sm) as pale yellow needles, mp 159–161 °C (acetone); R_f (CH_2Cl_2/pet. ether, 1:1) 0.37; ν_{max} ($CHCl_3$, neat)/cm^{-1} 2932, 2836, 1619, 1504, 1236, 1020; δ_H (400 MHz, $CDCl_3$) 7.96 (1H, d, *J* = 9.0, ArH), 7.50 (1H, s, ArH), 7.39 (1H, dd, *J* = 9.0, 2.5, ArH), 7.26 (1H, d, *J* = 2.5, ArH), 4.72 (2H, s, CH_2Br), 3.97 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 158.3 (4C), 145.0 (4C), 143.2 (4C), 138.3 (4C), 131.0 (CH), 126.1 (4C), 125.8 (CH), 123.0 (CH), 102.0 (CH), 55.7 (OCH_3), 27.6 (CH_2); *m/z* (EI) 329 [M^+] (^{79}Br × 2) (50%), 331 [M^++2] (^{79}Br, ^{81}Br) (100%), 333 [M^++2+2] (^{81}Br × 2) (48%), 250 [M^+-Br], (100%), 252 [M^++2−Br], (99%), 171 [M^+-Br_2]; HRMS (EI) $C_{11}H_9Br_2NO$ (M^+) requires: 328.9062; found: 328.9051.

4.4. (1*S*,3*S*,4*R*)-2-((2-Bromo-6-methoxyquinolin-4-yl)methyl)-3-((1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate 11

Sulfide **1** (1.0 g, 4.0 mmol) was added to a solution of dibromide **10** (0.662 g, 2.00 mmol) in CH_2Cl_2 (4.0 ml) followed by addition of a solution of $NaBF_4$ (1.10 g, 10.0 mmol) in water (2.0 ml, 5 M) and the resulting mixture was heated at 45 °C for 96 h. Water (30 ml) was added and the aq layer was extracted with CH_2Cl_2 (4 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The crude material was purified by passing though a short silica plug (eluting with CH_2Cl_2 and then with MeOH/CH_2Cl_2 1:9), which afforded the *sulfonium salt* **11** (0.92 g, 78%, 95% brsm) as light yellow foam; R_f (CH_2Cl_2/MeOH, 9:1) 0.32; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* = 9.2, ArH), 7.60 (1H, s, ArH), 7.36 (1H, dd, *J* = 9.2, 2.7, ArH), 7.15 (1H, d, *J* = 2.7, ArH), 5.13 (1H, d, *J* = 14.0, C*H*HS), 4.69 (1H, d, *J* = 14.0, CH*H*S), 4.37 (2H, br s., CHS, CHS), 4.00 (3H, s, OCH_3), 3.22 (1H, br s.), 2.94 (1H, d, *J* = 13.4), 2.50–2.55 (1H, m), 2.29 (1H, d, *J* = 13.0), 2.06–2.23 (3H, m), 1.98 (1H, d, *J* = 3.3), 1.79–1.89 (2H, m), 1.55–1.72 (2H, m), 1.25 (1H, ddd, *J* = 12.5, 9.2, 3.5), 1.18 (3H, s), 1.09 (3H, s), 1.02–1.08 (1H, m); δ_C (100 MHz, $CDCl_3$) 215.4 (C=O), 159.6 (4C), 144.5 (4C), 137.6 (4C), 135.1 (4C), 131.0 (CH), 127.5 (CH), 125.9 (4C), 124.6 (CH), 100.5 (CH), 70.5 (CH), 60.0 (4C), 59.5 (CH), 56.3 (CH_3), 50.0 (4C), 45.2 (CH), 44.0 (CH_2), 43.6 (CH), 42.7 (CH_2), 41.6 (CH_2), 33.6 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 24.5 (CH_2), 21.9 (CH_3), 19.0 (CH_3); *m/z* (ESI^+) 500 [M^+-BF_4], 502 [M+2−$BF_4]^+$, 284, 286, 250 [M−$BF_4-C_{15}H_{22}OS]^+$, 252 [M^++2−$BF_4-C_{15}H_{22}OS$]; HRMS (ESI^+) $C_{26}H_{31}{}^{79}BrNO_2S$ (M^+) requires: 500.1253; found: 500.1236.

4.5. (3*R*,4*S*)-2-(Trimethylsilyl)ethyl 4-(((2*R*,3*R*)-3-(2-bromo-6-methoxyquinolin-4-yl)oxiran-2-yl)methyl)-3-vinylpiperidine-1-carboxylate 16

Manually ground KOH (28.6 mg, 0.511 mmol) was added to a solution of sulfonium salt **11** (100 mg, 0.170 mmol) in CH_3CN/*t*-BuOH (1:5) (0.6 ml, 0.3 M) containing meroquinene 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. CH_3CN was evaporated under vacuum and water (10 ml) was added and the aq layer was extracted with EtOAc (4 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material (dr 93:7 *trans:trans*) was purified by flash silica gel column chromatography (Et_2O/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; R_f (Et_2O/pentane 1:1) 0.30; **16**: δ_H (400 MHz; acetone-d_6) 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, ddd, *J* = 17.3, 10.5, 8.8 Hz, C*H*=CHH), 5.18 (1H, ddd, *J* = 17.3, 2.1, 1.1 Hz, CH=C*H*H), 5.13 (1H, dd, *J* = 10.5, 2.1 Hz, CH=CH*H*), 4.45 (1H, dd, *J* = 2.0, 0.5 Hz, OC*H*–Ar), 4.11–4.17 (3H, m, $Me_3Si-CH_2-CH_2O$ and C*H*HN), 4.02–4.10 (1H, m, CH*H*N), 3.98 (3H, s, OCH_3), 3.15 (1H, ddd, *J* = 7.2, 4.0, 2.0 Hz, CH_2CH–OCH), 2.87–3.04 (1H, m, NC*H*H), 2.45–2.48 (1H, m, NCH*H*), 2.10–2.16 (1H, m, ring CH), 2.00 (1H, ddd, *J* = 14.3, 6.5, 4.0 Hz, CHO–C*H*HCH), 1.51–1.72 (4H, m, CHOCH*H*–CH and ring CH_2, CH), 0.96–1.02 (2H, m, $Me_3Si-CH_2-CH_2O$), 0.05 (9H, s, $SiMe_3$); δ_C (100 MHz; acetone-d_6) 159.4 (4C), 156.1 (N(O)C=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 (CH_2), 102.8 (CH), 63.6 (CH_2), 62.8 (CH), 56.3 (CH_3), 55.8 (CH), 49.0 (CH_2), 44.2 (CH_2), 43.5 (CH), 38.0 (CH), 36.3 (CH_2), 28.6 (CH_2), 18.4 (CH_2), −1.3 (CH_3 × 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 $MgSO_4$, 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 by aq NH_3, and extracted with EtOAc (4 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH 20:1 containing 0.75% Et_3N) to afford a mixture of quinine and quinidine (4:1, 50 mg, 73%) as a colorless solid, with spectroscopic data (^{1}H NMR, ^{13}C NMR) matching the reported data.[3a]

4.7. (1*S*,3*S*,4*R*)-2-((2-Bromo-6-methoxyquinolin-4-yl)methyl)-3-((1*R*,4*S*)-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 CH_2Cl_2 (6.0 ml) followed by the addition of a solution of $NaBF_4$ (1.65 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 CH_2Cl_2 (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The crude material was subjected to flash silica gel column chromatography (eluting with CH_2Cl_2 and then with MeOH/CH_2Cl_2 1:9), which afforded the *sulfonium salt* **17** (1.237 g, 70%, 95% brsm) as a light yellow foam; R_f (CH_2Cl_2/MeOH, 9:1) 0.31; ν_{max} ($CHCl_3$, neat)/cm^{-1} 2964, 1735 (C=O), 1619, 1556, 1506, 1239, 1020; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* = 9.2, ArH), 7.59 (1H, s, ArH), 7.36 (1H, dd, *J* = 9.2, 2.7, ArH), 7.16 (1H, d, *J* = 2.7, ArH), 5.14 (1H, d, *J* = 14.0, C*H*HS), 4.69 (1H, d, *J* = 14.0, CH*H*S), 4.33–4.41 (2H, m, CHS, CHS), 4.00 (3H, s, OCH_3), 3.22 (1H, br s.), 2.95 (1H, d, *J* = 13.4), 2.48–2.58 (1H, m), 2.29 (1H, d, *J* = 13.0), 2.06–2.23 (3H, m), 1.98 (1H, d, *J* = 3.3), 1.79–1.89 (2H, m), 1.55–1.72 (2H, m), 1.25 (1H, ddd, *J* = 12.5, 9.2, 3.5), 1.18 (3H, s), 1.10 (3H, s), 1.01–1.08 (1H, m); δ_C (100 MHz, $CDCl_3$) 215.4 (C=O), 159.6 (4C), 144.5 (4C), 137.6 (4C), 135.1 (4C), 131.0 (CH), 127.4 (CH), 125.9 (4C), 124.6 (CH), 100.5 (CH), 70.5 (CH), 60.0 (4C), 59.5 (CH), 56.3 (CH_3), 50.0 (4C), 45.2 (CH), 44.0 (CH_2), 43.6 (CH), 42.7 (CH_2), 41.6 (CH_2), 33.6 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 24.5 (CH_2), 21.9 (CH_3), 19.0 (CH_3 *m/z* (ESI$^+$) 500 [M$^+$−BF_4], 502 [M+2−BF_4]$^+$, 284, 286, 250 [M−BF_4−$C_{15}H_{22}OS$]$^+$, 252 [M$^+$+2−BF_4−$C_{15}H_{22}OS$]; HRMS (ESI$^+$) $C_{26}H_{31}{}^{79}BrNO_2S$ (M$^+$) requires: 500.1253; found: 500.1253.

4.8. (3*R*,4*S*)-2-(Trimethylsilyl)ethyl 4-(((2*S*,3*S*)-3-(2-bromo-6-methoxyquinolin-4-yl)oxiran-2-yl)methyl)-3-vinylpiperidine-1-carboxylate 18

Manually ground KOH (42 mg, 0.75 mmol) was added to a solution of sulfonium salt **17** (147 mg, 0.25 mmol) in CH_3CN/*t*-BuOH (1:5) (0.9 ml, 0.28 M) containing meroquinene aldehyde **6** (148 mg, 0.50 mmol) at 0 °C under an argon atmosphere. The resulting turbid yellow solution was stirred at 0 °C for 48 h. CH_3CN was evaporated under vacuum and water (10 ml) was added and the aq layer was extracted with EtOAc (4 × 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material (dr 89:11 *trans*/*trans*) was purified by flash silica gel column chromatography (Et_2O/pentane 1:2) to afford the mixture of *trans* epoxides **18**:**16** (90:10, 111 mg, 81%) as a light yellow gum; R_f (Et_2O/pentane 1:1) 0.30; **18**: δ_H (400 MHz; acetone-d_6) 7.89 (1H, d, *J* = 9.3 Hz, ArH), 7.55 (1H, d, *J* = 2.7 Hz, ArH), 7.46 (1H, dd, *J* = 9.3, 2.7 Hz, ArH), 7.34 (1H, d, *J* = 0.5 Hz, ArH), 5.89 (1H, ddd, *J* = 17.2, 10.4, 8.8 Hz, C*H*=CHH), 5.20 (1H, ddd, *J* = 17.2, 2.1, 1.0 Hz, CH=C*H*H), 5.13 (1H, dd, *J* = 10.5, 2.1 Hz, CH=CH*H*), 4.49 (1H, dd, *J* = 2.0, 0.5 Hz, OC*H*–Ar), 4.10–4.18 (3H, m, Me_3Si–CH_2–CH_2O and C*H*HN), 4.05–4.10 (1H, m, CH*H*N), 3.99 (3H, s, OCH_3), 3.12 (1H, ddd, *J* = 5.9, 5.9, 2.0 Hz, CH_2C*H*–OCH), 2.85–3.02 (1H, m, NC*H*H), 2.41–2.48 (1H, m, NCH*H*), 2.07–2.14 (1H, m, ring CH), 1.79–1.87 (1H, m, CHO–C*H*HCH), 1.66–1.76 (2H, m, CHOCH*H*–CH and ring CH), 1.51–1.64 (2H, m, ring CH_2), 0.95–1.02 (2H, m, Me_3Si–CH_2–CH_2O), 0.05 (9H, s, $SiMe_3$); δ_C (100 MHz; acetone-d_6) 159.4 (4C), 156.1 (N(O) C=O), 147.0 (4C), 145.1 (4C), 139.6 (4C), 137.0 (CH),, 131.4 (CH), 127.6 (4C), 123.7 (CH), 121.4 (CH), 117.6 (CH_2), 102.8 (CH), 63.6 (CH_2), 63.1 (CH), 56.3 (CH_3), 55.4 (CH), 49.0 (CH_2), 44.3 (CH_2), 43.9 (CH), 37.6 (CH), 36.5 (CH_2), 28.3 (CH_2), 18.4 (CH_2), −1.2 (CH_3 × 3).

4.9. Quinidine

CsF (111 mg, 0.731 mmol) was added to a solution of epoxides **18**:**16** (4.2:1 *trans*/*trans*, 80.0 mg, 0.146 mmol) in DMF/*t*-BuOH (9:1, 1.0 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 $MgSO_4$, 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 NH_3, and extracted with EtOAc (4 × 10 ml). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH 20:1 containing 0.75% Et_3N) to afford a mixture of quinidine and quinine (4.2:1, 34 mg, 72%) as colorless solid, with spectroscopic data (^{1}H NMR, ^{13}C NMR) matching the reported data.[3a]

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