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Note

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Tricyclic quaternary ammonium salts derived from *Cinchona* alkaloids

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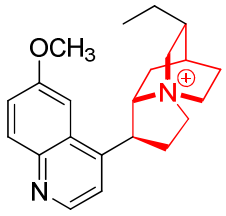
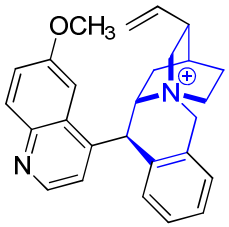
Abstract



1-azoniatricyclo[5.2.2.0^{1,5}] undecane system



1-azoniatricyclo[6.2.2.0^{1,6}] dodecane system

Tricyclic systems with quaternary bridgehead nitrogen atoms are rare but interesting class of compounds. Chiral quinuclidine derivative salts with fused five and six-membered rings (X-ray) were obtained via modification of *Cinchona* alkaloids. The ease of ring formation was dependent on its size, while even mild activation sufficed to close the five membered ring. On the other hand the systems with fused benzene and a six-membered ring formed atropisomers separated by a barrier of ca. 15 kcal/mol, whose interconversion was studied by DFT and NMR.

Tricyclic systems with bridgehead quaternary nitrogen atom are both rarely synthesised,[1] and seldom found in nature. Natural products incorporating 1-azonia-tricyclo-[5.2.1.$0^{1,5}$]decane, [5.2.2.$0^{1,5}$]undecane and [6.2.2.$0^{1,6}$]dodecane systems have been identified in few *Daphniphyllum*,[2] and indole alkaloids[3,4] (Figure 1). These constitute minor alkaloids, which were isolated in yields of 0.002–0.02% from *Daphnyllium glaucescens*,[2] *Hunteria eburnean*,[3] and *Ophiorrhiza major* species.[4] Also the tricyclo[5.2.2.$0^{1,5}$]undecane ring system is fairly uncommon.[5]

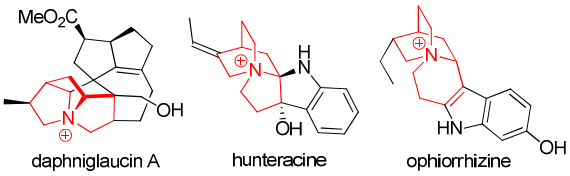
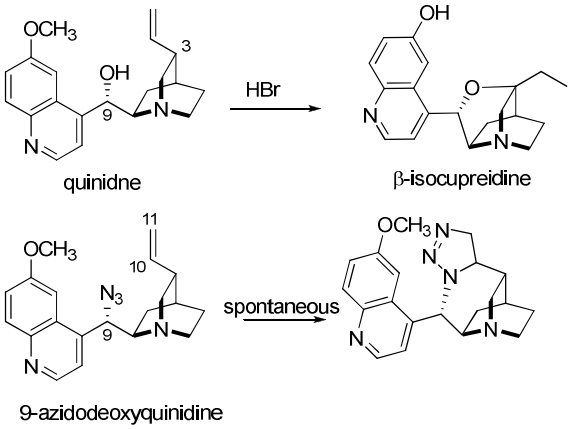


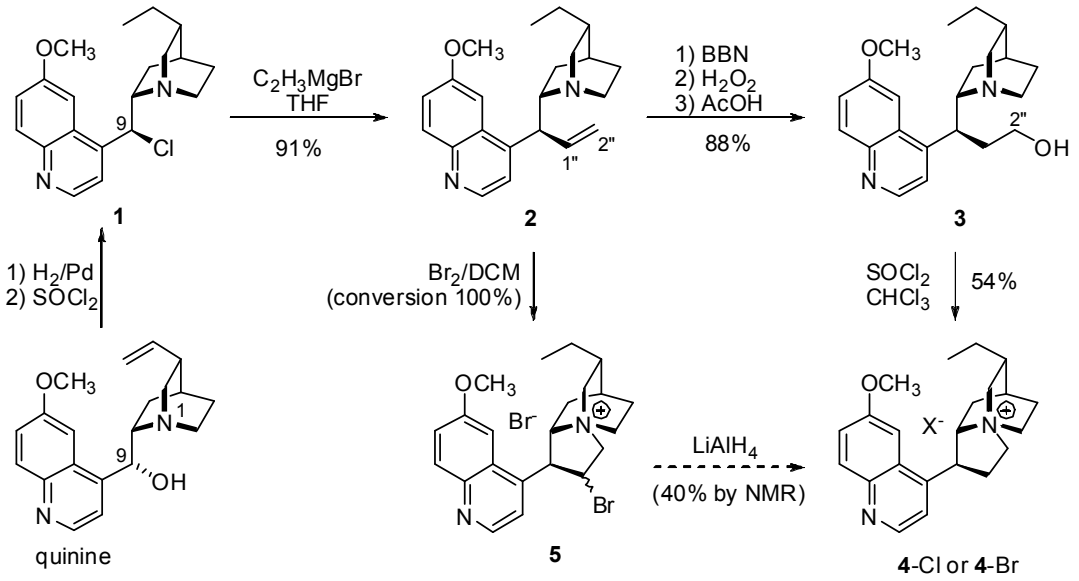
Figure 1. Naturally occurring cations of *Daphniplhyllium*, *Hunteria* and *Ophiorrhiza* alkaloids

Such ring systems could be constructed based on the quinuclidine present in various *Cinchona* alkaloids. In our previous report we introduced three and five-membered rings incorporating the C-9 atom, independently of the existing ring systems.[6] However, there are only few synthetic derivatives with additional heterocyclic rings fused to the quinuclidine system. The corresponding connections were previously made by exploiting the reactivity of 3-vinyl group with substituents at position 9: the natural hydroxyl group or azide residue. Such products were obtained only for alkaloids of 8*R*,9*S* configuration (like in quinidine), where the two reactive groups can come in close contact (Scheme 1).[7,8] One of such products, β-isocupreidine (β-ICD) is a long recognized catalyst particularly effective in the Baylis-Hillman reaction.[9] There are no convincing reports[10] of derivatives incorporating quinuclidine nitrogen atom in the extension of the ring system. Thus, we propose unique derivatives of *Cinchona* alkaloids by extending aza-bicyclo[2.2.2]octane cage to a tricyclic system with central quaternary nitrogen atom.



Scheme 1. Examples of syntheses of fused rings involving the C-9 atom, and proposed new structures of quinine and quinidine series

Aiming at the synthesis of a carbon-only bridge between the quinuclidine nitrogen N-1 atom and the C-9 atom of *Cinchona* alkaloids we followed our previously published procedure for the coupling of sp^2-Grignard reagents with 9-chloro-10,11-dihydroquinine (**1**).[11] The reaction of the alkaloid chloroderivative **1** with carefully controlled excess of vinyl magnesium bromide provided the 9-vinyl derivative **2** in improved 91% yield. Subsequent Brown hydroboration with BBN and oxidation provided the corresponding primary alcohol **3** in very good yield. However, application of borane in complex with dimethylsulfide or triethylamine instead of BBN did not provide **3** (likely due to formation of azaborolidines). Initially we considered a stepwise transformation of alcohol **3** to the quaternary salt **4**, by converting the hydroxyl to a better leaving group with methanesulfonyl or thionyl chlorides. It was found that on derivatization of the hydroxyl group in **3**, the intermediate undergoes spontaneous ring closure (Scheme 2).



Scheme 2. Synthesis of 1-azonia-tricyclo[5.2.2.0^{1,5}]undecane system

In fact application of all the activating conditions tried led to **4** (for the details, see SI).[12] Even under Mitsunobu-type transformations, which rarely lead to nitrogen quaternization,[13] the reaction of external nucleophile was barely noticeable in the MS of crude reaction mixtures in contrast to the competing intramolecular cyclization. Although the isolated yields (20-54%, Table S1, SI) appear moderate or low, the loss of material was mostly attributed to the difficulty in separating the crystalline product. In the reaction with thionyl chloride the product **4**-Cl initially separates from the reaction mixture with additional molecule of hydrochloric acid. The salt **4**-Cl·HCl is insoluble in most organic solvents, thus isolation was greatly facilitated.

In an alternative approach the vinyl derivative **2** was brominated using a solution of Br_2 in DCM to form a mixture of brominated quaternary salts **5**. Without separating the components, the mixture was directly reduced with $LiAH_4$ to give **4**-Br. Although the pathway via compound **5** seemed attractive, the obtained product **4** had observable contaminants. The structure of the product **4** was elucidated based on NMR data, and unambiguously confirmed with single crystal X-ray study of **4**-Cl (Figure 2). The chloride anion in **4**-Cl, can be replaced with tetrafluoroborate to give **4**-BF_4, which is no longer hygroscopic and can be stored on air for at least two years.

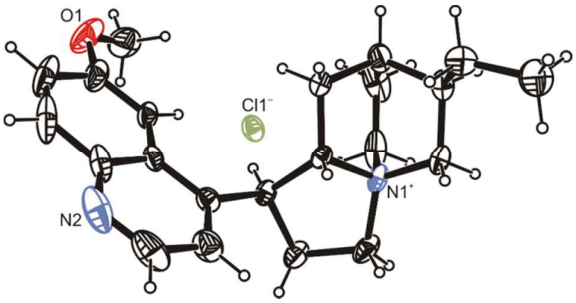
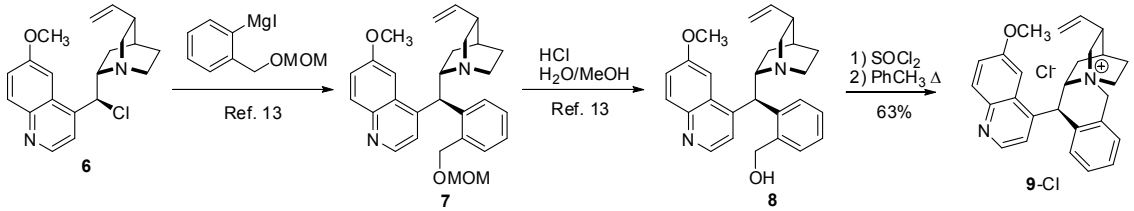


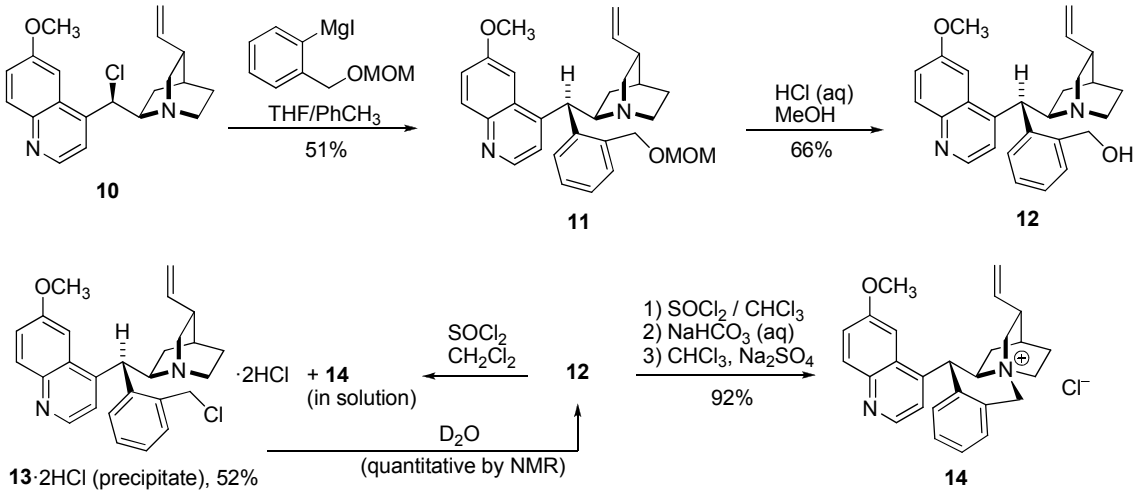
Figure 2. X-ray structure of **4**-Cl; thermal ellipsoids are shown at the 20% probability level

In addition to the product **4** with fused five membered ring, we planned to obtain quaternary salts with fused six membered ring analoguous to *N*1-benzylated alkaloids. Thus following our procedure 9-chloroquinine (**6**) was coupled with *o*-(methoxymethoxymethyl)phenylmagnesium iodide to give the corresponding arylated product **7**.[14] The methoxymethoxy group (MOM) was hydrolysed with aqueous/methanolic hydrochloric acid to give benzyl alcohol derivative **8**.[14] Subsequent reaction with thionyl chloride led directly to the ring fusion by quaternization of the *N*1 nitrogen atom. Unlike for the synthesis of five membered ring in **4**, here the crude reaction mixture contained some intermediate product with hydroxyl group replaced with chlorine atom, which could be observed in the ESI-MS (see SI). Nevertheless, brief heating of the crude mixture suspended in toluene led to conversion of this intermediate product to **9** (Scheme 3).



Scheme 3. Synthesis of quinine-based 1-azonia-tricyclo[6.2.2.0^{1,6}]dodecane system

The reaction steps used to obtain quinine-derived **9**-Cl were also applied for the synthesis of quinidine analogue. Comparably, the substitution of the quinidine chloroderivative **10** with respective Grignard reagent required higher temperature and extended reaction time to obtain **11**. Hydrolysis of MOM ether **11** was achieved as previously. On subsequent treatment of the solution of alcohol **12** with thionyl chloride, the dihydrochloride of chloroderivative **13** was the major solid product separating from the reaction mixture. When the solid **13**·2HCl was dissolved in D_2O the benzyl-type chloride underwent slow hydrolysis back to **12**, the reaction was quantitative after 72 h. Following hydrolysis, no cyclization product **14** was observed in the NMR, but it remained detectable by ESI-MS. In another experiment, following the treatment of **12** with thionyl chloride, the entire reaction suspension was alkalized with sodium bicarbonate, and the cyclization reaction was allowed to complete in organic solvent without water. This time cyclization toward **14** proceeded selectively and the product was obtained in high yield (Scheme 4). The dissimilarities between the reactions of **8** and **12** with $SOCl_2$ most likely originate from different solubility of products, intermediates and their hydrochloride salts.



Scheme 4. Synthesis of quinidine-based 1-azonia-tricyclo[6.2.2.0^{1,6}]dodecane system

Both quinine and quinidine derivatives with new six-membered rings **9** and **14** exhibit atropisomers at the NMR time scale. They display two sets of signals both in ^{1}H and ^{13}C NMR in ratios of 2:1 to 3:1.

For **9** in $CDCl_3$ at elevated temperatures (up to 318K) the corresponding signals of the rotamers broadened and their distance slightly decreased. For a suspension of **14**-Cl in D_2O, coalescence of most signals was eventually achieved at about 328K. The equilibrium of the two rotamer populations was confirmed by positive phase correlation signals in the EXSY experiment (For the details, see SI). The atropisomerism of cations **9** and **14** was further investigated by theoretical calculation. On inspection of molecular model, the highly fused ring system appears rigid, while the pendant methoxyquinoline ring can be rotated along the C9-C4' single bond with few conflicts. For cation **9** the scan of this coordinate (C^{Ar}-C9-C4-C3' dihedral) using fast semiempirical computation (PM6) revealed two low energy conformers at about +60 and –120° (*syn* and *anti*), along with two high energy conformations at about –45° and +120°. The calculation was repeated for **14**, and it behaved like an enantiomer of **9**. The gas-phase *syn* and *anti* conformers of the isolated cations were then calibrated at the DFT/B3LYP/6-31G(d,p) level of theory to local minima (Figure 3, for details see SI). Then two transition states were calculated following the QST3 algorithm at the same level of theory assuming the two high energy PM6 conformations as the initial transition state guess. The DFT calculation revealed that *syn* and *anti* conformers are essentially equal in energy (ΔE up to 0.3 kcal/mol). From the solution equilibria observed in chloroform for **9**-Cl and **14**-Cl (K_{eq} of about 0.5 and 0.36, respectively) the experimental energy differences between the conformers were also rather low (ΔG = 0.4 and 0.6 kcal/mol, respectively) and in good agreement with the DFT results. The energy barrier states were 15.9 and 19.1 kcal/mol higher in energy than the stable conformers for **9**. For quinidine derivative **14** the corresponding states were estimated at 14.1 and 18.1 kcal/mol. The lower barriers (15.9 and 14.1 kcal/mol) between the interconverting atropisomers are well reproduced by the observed behaviour in the variable temperature NMR. For **14**-Cl in D_2O suspension coalescence of signals occurs between 318 and 338 K translating to a rotation barrier of 15.8±0.3 kcal/mol.

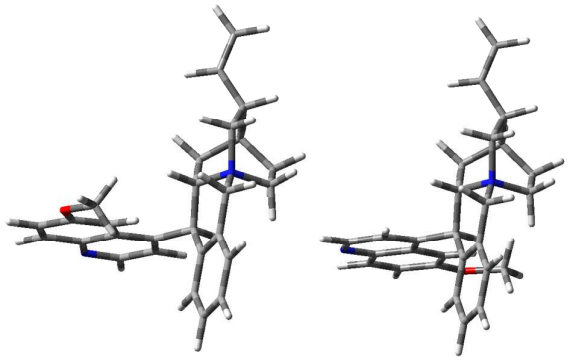


Figure 3. DFT calculated structures of rotamers of cation **9**

The quaternary ammonium salts of *Cinchona* derivatives are often employed in asymmetric synthesis as either phase transfer catalysts, or a direct source of nucleophilic anions.[15-16] Also, as opposed to simple 1-benzyl derivatives, the tricyclic system is very rigid. However, despite a few attempts (see SI), we were not able to demonstrate the applicability of the obtained products in PTC. We infer that the tricyclic systems assume nearly spherical symmetry surrounding the positive charge thereby spoiling the enantioselectivity of catalysed reactions.

In summary we have shown the formation of tricyclic derivatives of *Cinchona* alkaloids by closing additional five and six-membered rings. While in the synthesis of six membered rings the ε-electrophilic derivatives could often be observed and isolated, any electrophilic character at the δ (2") carbon resulted to an immediate ring closure.

Experimental

Improved synthesis of **(8*S*,9*S*)-10,11-dihydro-6'-methoxy-9-vinyl-cinchonan (2).** 9*S*-chloro-9-deoxy-10,11-dihydroquinine (**1**, 5.08 g, 14.7 mmol) was dissolved in dry THF (33 mL), and a solution of vinylmagnesium bromide (20.6 mL, 1 M, 1.4 equiv) was added. The mixture was stirred at 50 °C for 24 h. Then, it was cooled in ice bath and ammonia buffer was added. The mixture was extracted

with $CHCl_3$, dried over Na_2SO_4 and evaporated. The residue was purified on silica gel ($CHCl_3$/MeOH 20:1 v/v) to give 4.52 g (91%) of **2** as colorless oil. Spectral data in accordance to the reported.[11]

(8*S*,9*S*)-10,11-Dihydro-9-(2-hydroxyethyl)-6'-methoxy-cinchonan (3). (8*S*,9*S*)-10,11-Dihydro-6'-methoxy-9-vinyl-cinchan (2.49 g, 7.41 mmol) was dissolved in THF (50 mL). A solution of BBN (32 mL, 0.5 M soln. in THF, 16.0 mmol, 2.16 equiv) was added. The mixture was stirred at 66 °C for 21 h. Then the mixture was cooled to room temperature and NaOH (45 mL, 20% aqueous), and hydrogen peroxide (7 mL, 30%, 68.5 mmol, 9.24 equiv) were added and stirring was continued for another 24 h. The mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated. The residue was dissolved in a mixture of diethyl ether and CH_2Cl_2 (60 mL) and washed twice with 10% aqueous NaOH. The product was extracted with aqueous HCl (2M, 4 × 10 mL). The acid extracts were basified with 10% aqueous NaOH and extracted into CH_2Cl_2 and dried over Na_2SO_4. The mixture was filtered through a pad of silica gel ($CHCl_3$ / MeOH 5:1). Obtained 2.31 g (88%) of **3** as colorless oil. $[\alpha]_D^{21}$ = +45 (*c* 1.03, CH_2Cl_2). ^{1}H-NMR (600 MHz, $CDCl_3$) δ, 8.68 (d, *J* = 4.6 Hz, 1H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.32 (d, *J* = 2.5 Hz, 1H), 7.17 (d, *J* = 4.6 Hz, 1H), 3.94 (s, 3H), 3.66-3.69 (m, 1H), 3.53-3.62 (m, 2H), 3.21-3.26 (m, 1H), 3.21 (dd, *J* = 13.6, 10.0 Hz, 1H), 3.12 (q, *J* = 9.2 Hz, 1H), 2.80-2.86 (m, 1H), 2.55-2.59 (m, 1H), 1.81-2.01 (m, 2H), 1.41-1.60 (m, 6H), 1.29-1.37 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.58-0.62 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 158.0, 148.8, 147.8, 144.7, 132.1, 128.3, 121.0, 119.1, 101.5, 61.6, 60.3, 57.0, 55.6, 42.8, 41.3, 40.9, 37.0, 28.18, 28.13, 27.8, 25.3, 12.1. HRMS (ESI-TOF) calcd. for $[C_{22}H_{30}N_2O_2+H]^+$ m/z: 355.2380, found: 355.2374

(1*R*,4*S*,5*S*,7*S*,8*R*)-1-Azonia-8-ethyl-4-(6-methoxyquinolin-4-yl)tricyclo[5.2.2.0^{1,5}]undecane chloride (4-Cl). Hydroxyethyl derivative **3** (470 mg, 1.33 mmol) was dissolved in a freshly distilled, ethanol-free $CHCl_3$ (16 mL). The mixture was cooled to 0 °C and thionyl chloride (0.20 mL, 2.7 mmol, 2.1 equiv) was added. The mixture was stirred for 24 h, while a crystalline precipitate forms. The precipitate, containing mostly **4**-Cl hydrochloride was centrifuged, and washed with diethyl ether (3 × 5 mL). The solid was suspended in aqueous $NaHCO_3$ solution (15 mL, 5%) and extracted with $CHCl_3$ (5 × 10 mL). The aqueous phase was concentrated to dryness and extracted (solid/liquid) with a mixture of $CHCl_3$/MeOH (10:1 v/v). The combined extrcts were dried over Na_2SO_4 and evaporated.

Obtained 294 mg (54%) of amorphous hygroscopic solid. A sample for X-ray study was recrystallized from MeOH/Et_2O. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.4 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.50 (d, J = 2.9 Hz, 1H), 7.46 (d, *J* = 4.8 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.6 Hz, 1H), 4.47 (m, 1H), 4.39 (m, 1H), 4.17-4.23 (m, 2H), 4.09 (m, 1H), 4.05 (s, 3H), 3.82-3.93 (m, 2H), 3.51 (m, 1H), 3.06 (m, 1H), 1.94-2.21 (m, 6H) 1.68 (dd, *J* = 13.6, 8.1 Hz, 1H) 1.56 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 158.1, 147.5, 143.9, 143.6, 131.1, 128.3, 121.9, 118.2, 102.2, 77.4, 69.5, 63.1, 61.0, 56.4, 51.6, 41.7, 36.8, 29.5, 26.7, 25.5, 24.2, 11.5 ppm. HRMS (ESI-TOF) calcd. for $[C_{22}H_{29}N_2O]^+$ m/z: 337.2274, found: 337.2279

4-Cl hydrochloride: ^{1}H NMR (600 MHz, D_2O): δ 8.95 (d, *J* = 6.0 Hz, 1H), 8.23 (d, *J* = 9.3 Hz, 1H), 8.08 (d, *J* = 5.9 Hz, 1H), 7.89 (dd, *J* = 9.3, 2.4 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 4.34 (m, 1H), 4.11 (m, 1H), 4.09 (s, 3H), 3.87 (m, 1H), 3.75 (m, 1H), 3.48 (m, 1H), 3.40 (m, 1H), 3.25 (m, 1H), 3.06 (m, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 2.06 (m, 1H), 2.03 (m, 1H), 1.97 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.45 (m, 1H), 1.39 (m, 1H), 1.02 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75.5 MHz, D_2O): δ 161.0, 157.0, 140.9, 134.0, 131.1, 127.8, 123.5, 121.1, 103.8, 61.4, 58.4, 56.8, 56.5, 42.0, 40.1, 36.5, 34.4, 26.0, 25.3, 24.4, 24.0, 11.0 ppm.

(1*R*,4*S*,5*S*,7*S*,8*R*)-1-Azonia-8-ethyl-4-(6-methoxyquinolin-4-yl)tricyclo[5.2.2.0^{1,5}]undecane tetrafluoroborate (4-BF_4). **4**-Cl (130 mg, 0.35 mmol) was suspended in MeCN (5 mL), and $NaBF_4$ was added (183 mg, 1.7 mmol, 4.8 equiv). The mixture was stirred for 24 h, and then evaporated. The residue was suspended in water (1 mL) and extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated. The residue was recrystallized from CH_2Cl_2 / Et_2O. Obtained 125 mg (85%) of **4**-BF_4 as white solid, stable on air. Mp (CH_2Cl_2 / Et_2O) 188–190 °C, $[\alpha]_D^{23}$ = –38 (*c* 0,9, 96% EtOH). IR (KBr): 3431, 2967, 2937, 1621, 1510, 1476, 1458, 1435, 1364, 1234, 1055, 1027, 913, 849 cm^{-1}

(1*S*,3*R*/*S*,4*S*,5*S*,7*S*,8*R*)-1-Azonia-3-bromo-8-ethyl-4-(6-methoxyquinolin-4-yl)tricyclo[5.2.2.0^{1,5}]undecane bromide (5-Br). 9-Vinyl derivative **2** (552 mg, 1.54 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. Then a solution of bromine in CH_2Cl_2 (0.54 mL, 2.9M, 1.56 mmol, 1.0 equiv) was added, and the mixture stirred for 0.5 h and then the volatiles were removed in vacuo to obtain **5**-Br isomer mixture. HRMS (ESI) calcd. for $[C_{22}H_{28}BrN_2O]^+$ m/z:

415.1380, found: 415.1387. The product was directly reduced with $LiALH_4$ (2.3 equiv) in THF to form **4**-Br.

(1*S*,5*S*,6*S*,8*S*,9*R*)-1-Azonia-5-(6-methoxyquinolin-4-yl)-9-vinyl-benzo[3,4]tricyclo[6.2.2.0^{1,6}]dodacane chloride (9-Cl). 9-(2-Hydroxymethylphenyl)-6'-methoxycinchonan (103 mg, 0.25 mmol)[14] was dissolved in a freshly distilled ethanol-free $CHCl_3$ (1 mL) and cooled to 0 °C. Then thionyl chloride (35 μL, 0.48 mmol, 1.9 equiv) was added, and the mixture was allowed to attain room temperature and stirred for 24 h. The volatiles were removed *in vacuo*, and the residue was suspended in 5% $NaHCO_3$ solution (0.5 mL). The product was extracted with $CHCl_3$/MeOH (10/1, v/v, 8 × 10 mL). Na_2SO_4 was added to the aqueous fraction and additional extraction was performed. The combined extracts were evaporated. The mixture containing the product and chlorobenzyl intermediate was suspended in toluene and heated at 100 °C for 12 h. The fine solid was separated by centrifugation, washed with toluene, and evacuated under vacuum. Obtained 68 mg (63%) of off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) *anti* rotamer (major): δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.58 (d, *J* = 4.5 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.22-7.25 (m, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 5.80 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.63 (d, *J* = 15.5 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 15.5 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 5.06-5.08 (m, 2H), 4.61-4.65 (m, 1H), 4.20-4.24 (m, 1H), 4.09-4.14 (m, 1H), 3.99 (s, 3H), 3.79-3.83 (m, 1H), 3.05-3.11 (m, 1H), 2.18-2.30 (m, 2H), 2.13 (br., 1H), 2.03 (br., 1H), 1.27-1.30 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) *anti* rotamer (major): δ 159.1, 148.6, 144.7, 143.8, 135.8, 134.8, 132.6, 129.5, 128.8, 128.6, 128.2, 127.6, 126.8, 122.9, 121.6, 118.4, 100.9, 64.8, 62.5, 61.5, 56.1, 49.2, 42.5, 37.7, 27.0, 25.5, 25.1; *syn* rotamer (minor): δ 157.8, 147.1, 145.8, 140.1, 135.8, 133.5, 132.3, 129.5, 128.6, 128.1, 127.8, 126.5, 126.1, 125.7, 122.4, 118.4, 102.6, 63.4, 62.7, 61.8, 55.5, 52.2, 49.1, 37.5, 26.9, 25.9, 24.8. HRMS (ESI-TOF) calcd. for $[C_{27}H_{29}N_2O]^+$ m/z: 397.2274, found: 397.2272

(8*R*,9*S*)-9-(2-(Methoxymethoxymethyl)phenyl)-6'-methoxycinchonan (11). To a solution of 2-methoxymethoxymethylphenylmagnesium iodide obtained from magnesium (205 mg, 8.44 mmol, 1.61 equiv) and *o*-iodobenzyl alcohol MOM ether (2.18 g, 7.85 mmol, 1.5 equiv) in THF (30 mL) was

added a solution of 9R-chloro-9-deoxy-quinidine (1.79 g, 5.22 mmol; mp. 134-136°C) in toluene (15 mL). The mixture was refluxed for 30 h, then cooled to room temperature and quenched with aqueous NH_4Cl and NaOH solutions. The mixture was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified on silica gel (CH_2Cl_2 / MeOH 20:1) to give 1.23 g (51%) of **11** as yellow solid (mp. 111–116 °C) and used directly to obtain **12**. A sample was recrystallized from EtOAc/hexane to give white crystalline solid: Mp. 118-120 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.9 Hz, 1H), 7.99 (d, *J* = 9.3 Hz, 1H), 7.87 (d, *J* =2.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.41-7.44 (m, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.23 (d, *J* = 4.9 Hz, 1H), 7.17-7.18 (m, 2H), 5.97 (ddd, *J* = 17.2, 10.5, 6.5 Hz, 1H), 5.57 (d, *J* = 10.6 Hz, 1H), 5.11 (dt, *J* =17.2, 1.5 Hz, 1H), 5.09 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.63 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.26 (d, *J* = 12.5 Hz, 1H), 4.07 (s, 3H), 3.59-3.64 (m, 1H), 3.33 (s, 3H), 2.87-3.09 (m, 4H), 2.22-2.27 (m, 1H), 1.63 (br. s, 1H), 1.52-1.61 (m, 2H), 1.37-1.41 (m, 1H), 0.96-1.00 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.3, 147.7 (2C overlapped), 144.9, 142.2, 141.1, 136.0, 131.9, 131.1, 129.5, 128.8, 127.7, 126.6, 122.2, 121.7, 114.5, 101.5, 94.4, 67.1, 59.6, 55.54, 55.46, 49.3, 47.5, 41.8, 39.7, 28.0, 26.6, 26.3. HRMS (ESI-TOF) calcd. for $[C_{29}H_{34}N_2O_3+H]^+$ m/z: 459.2642, found: 459.2636

(8*R*,9*S*)-9-(2-(Hydroxymethyl)phenyl)-6'-methoxycinchonan (12). MOM ether **11** (982 mg, 2.14 mmol) was dissolved in a mixture of MeOH (50 mL) and aqueous HCl (36%, 20 mL). The mixture was stirred for 24 h at r.t. and evaporated *in vacuo*. The residue was suspended in a mixture of aqeous ammonia and CH_2Cl_2, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated. The residue was purified on silica gel ($CHCl_3$ / MeOH 15:1) to give 584 mg (66%) of off-white crystallizing solid. Mp. 217–219 °C (dec.); $[\alpha]_D^{21}$ = +186 (*c* 0.90, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.7 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.52 – 7.54 (m, 2H), 7.36 (d, *J* = 4.7 Hz, 1H), 7.31 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.25 (td, *J* = 7.7, 1.3 Hz, 1H), 7.22 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.14 (td, *J* = 7.6, 1.0 Hz, 1H), 5.81 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1H), 5.44 (d, *J* = 10.6 Hz, 1H), 5.04 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.00 (dt, *J* = 10.4, 1.2 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.3 (br. 1H, OH), 3.94 (s, 3H), 3.58 (q, *J* = 9.5 Hz, 1H), 2.96 – 3.06 (m, 2H), 2.87 – 2.92 (m, 1H), 2.76 – 2.81 (m, 1H), 2.22 – 2.26 (m, 1H), 1.67 – 1.69 (m, 1H), 1.60 – 1.65 (m, 1H), 1.52 – 1.57 (m, 1H), 1.42 – 1.47 (m,

1H), 1.28 – 1.32 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.2, 147.1, 146.7, 144.7, 140.8, 140.0, 139.7, 131.7, 130.3, 129.1, 128.4, 128.0, 127.1, 122.0, 121.6, 115.0, 101.2, 63.6, 61.0, 55.5, 49.0, 47.7, 42.0, 39.4, 28.2, 27.1, 26.0. HRMS (ESI-TOF) calcd. for $[C_{27}H_{30}N_2O_2+H]^+$ m/z: 415.2380, found: 415.2379

(8*R*,9*S*)-9-(2-(Chloromethyl)phenyl)-6'-methoxycinchonan (13) dihydrochloride. 9-(2-Hydroxymethylphenyl)-quinidine (170 mg, 0.41 mmol) was dissolved in a CH_2Cl_2 (10 mL) and cooled to 0 °C. Then thionyl chloride (40 µL, 0.55 mmol, 1.3 equiv) was added, and the mixture was allowed to warm to room temperature and kept for 24 h. A precipitate formed, which was separated by centrifugation. Obtained 108 mg of white hygroscopic solid of **13**·2HCl (52%). ^{1}H NMR (600 MHz, D_2O): δ 8.73 (d, *J* = 5.8 Hz, 1H), 8.13 (d, *J* = 9.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 5.9 Hz, 1H), 7.84 (s, 1H), 7.79 (d, *J* = 9.4 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.35 – 7.40 (m, 2H), 5.87 (ddd, *J* = 17.4, 10.7, 4.4 Hz, 1H), 5.74 (d, *J* = 11.5 Hz, 1H), 5.28 (d, *J* = 10.7 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 4.79 – 4.84 (m, 1H), 4.48 (d, *J* = 12.2 Hz, 1H), 4.39 (d, *J* = 12.2 Hz, 1H), 4.09 (s, 3H), 3.54-3.64 (m, 2H), 3.46 – 3.50 (m, 1H), 3.26 – 3.32 (m, 1H), 2.77 – 2.81 (m, 1H), 2.02 – 2.04 (m, 1H), 1.92 – 2.00 (m, 2H), 1.54 – 1.58 (m, 1H), 1.42 – 1.47 (m, 1H). ^{13}C NMR (151 MHz, D_2O) δ 161.3, 153.3, 140.2, 136.92, 136.88, 135.2, 134.3, 132.6, 131.4, 130.2, 129.9, 128.4, 126.8, 123.5, 122.7, 116.8, 101.0, 60.1, 56.6, 49.2, 47.1, 45.1, 40.9, 35.2, 25.7, 23.9, 21.9 ppm. HRMS (ESI-TOF) calcd. for $[C_{27}H_{29}N_2OCl+H]^+$ m/z: 433.2041, found 433.2033. Anal. calcd for $C_{27}H_{29}N_2OCl·2HCl$: Cl, 21.02; found: Cl, 22.7.

(1*S*,5*R*,6*R*,8*S*,9*R*)-1-Azonia-5-(6-methoxyquinolin-4-yl)-9-vinyl-benzo[3,4]tricyclo[6.2.2.0^{1,6}]dodacane chloride (14). 9-(2-Hydroxymethylphenyl)-quinidine (67 mg, 0.16 mmol) was dissolved in a freshly distilled ethanol-free $CHCl_3$ (4 mL) and cooled to 0 °C. Then solution of thionyl chloride (0.5 mL, 80 mg/mL in $CHCl_3$, 0.33 mmol, 2.1 equiv) was added, and the mixture was allowed to attain room temperature and stirred for 20 h. Saturated $NaHCO_3$ solution (0.7 mL) was added, and the mixture was diluted with $CHCl_3$ (20 mL), after 5 min, solid Na_2SO_4 was added until no liquid aqueous phase was visible. Then the solid was washed with $CHCl_3$ (2 × 10 mL) and then with $CHCl_3$ / MeOH (5:1, 2 × 15 mL). The combined organic phases were dried over Na_2SO_4

and evaporated to afford 65 mg (92%) light-brown solid film of **14**. ^{1}H NMR (151 MHz, $CDCl_3$, 288K) *anti* rotamer (major): δ 8.66 (d, *J* = 4.4 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 4.4 Hz, 1H), 7.41 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.25-7.29 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 6.02 (ddd, *J* = 17.2, 10.7, 4.5 Hz, 1H), 5.63 (d, *J* = 15.3 Hz, 1H), 5.34 (d, *J* = 10.7 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 15.3 Hz, 1H), 4.97-5.00 (m, 2H), 4.38-4.48 (m, 2H), 4.27 (t, *J* = 12.2 Hz, 1H), 3.94 (s, 3H), 3.50-3.58 (m, 1H), 3.10 (br., 1H), 2.10-2.24 (m, 3H), 1.87-1.92 (m, 1H), 1.59-1.63 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$, 288K) *anti* rotamer (major): δ 158.9, 148.6, 144.6, 144.3, 138.8, 134.3, 132.7, 129.5, 128.9, 128.19, 128.14, 127.6, 126.6, 123.0, 121.9, 117.3, 100.7, 64.1, 62.0, 58.9, 53.3, 55.7, 42.4, 36.6, 26.5, 25.5, 25.2; *syn* rotamer (minor): δ 157.6, 147.0, 145.7, 140.4, 138.3, 132,9, 132.2, 129.5, 128.6, 127.8, 127.6, 126.3, 125.5, 125.3, 122.3, 117.3, 102.6, 62.2, 61.8, 59.5, 55.6, 53.5, 50.4, 36.5, 26.6, 25.3, 25.0. HRMS (ESI-TOF) calcd. for $[C_{27}H_{29}N_2O]^+$ m/z: 397.2274, found 397.2284

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Supporting information available

Computational details, supporting Tables and Figures, plots of NMR experiments, crystallographic data file (CIF) for **4**-Cl.

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