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Remote Control of the C-3–C-4 Double-Bond Epoxidation of a Chiral 1,2-Dihydroquinoline: Application to the Synthesis of (–)-(*R*)-Sumanirole (PNU-95666E)

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A twelve-step synthesis of (–)-(*R*)-sumanirole starting from quinoline is described. The first synthetic approach, using a chiral Reissert adduct, was too problematic to be pursued further. In the second successful approach, the authors took advantage of the stereoselective epoxidation of a 1,2-dihydroquinoline bearing an Evans' chiral auxiliary at N-1.

Introduction

1,2,3,4-Tetrahydroquinolines (1,2,3,4-THQs) have been the subject of continuous investigations over the years. The marked interest in these compounds is due to the 1,2,3,4-THQ scaffold being present in the framework of numerous biologically interesting natural products and many important pharmacological drugs. Additionally, free 1,2,3,4-THQs (i.e., not fused to another ring) exhibit a broad range of biological activities. Consequently, synthetic methodologies for preparing diversely substituted 1,2,3,4-THQ derivatives have attracted considerable interest, and several efficient methods have been reported.[1] With regard to total synthesis, we are interested in 1,2,3,4-THQs bearing an NHR or an NR^1R^2 substituent at C-3 or C-4. Four selected examples are shown in Figure 1. Sumanirole, [PNU-95666; (*R*)-**1**] is a highly selective D2 receptor full agonist, which was developed for the treatment of Parkinson's disease and restless leg syndrome.[2] Anachelin H (**2**)[3] is an iron chelator, isolated from the cyanobacterium *Anabaena cylindrica*. The *N*,*N*-dimethylquinolinium chromophore is believed to serve as a tyrosinase activator. Anachelin H also exhibits moderate antibiotic activity against *Moraxella catarrhalis*. Torcetrapib (CP-529414; **3**)[4] was developed to treat hyper-

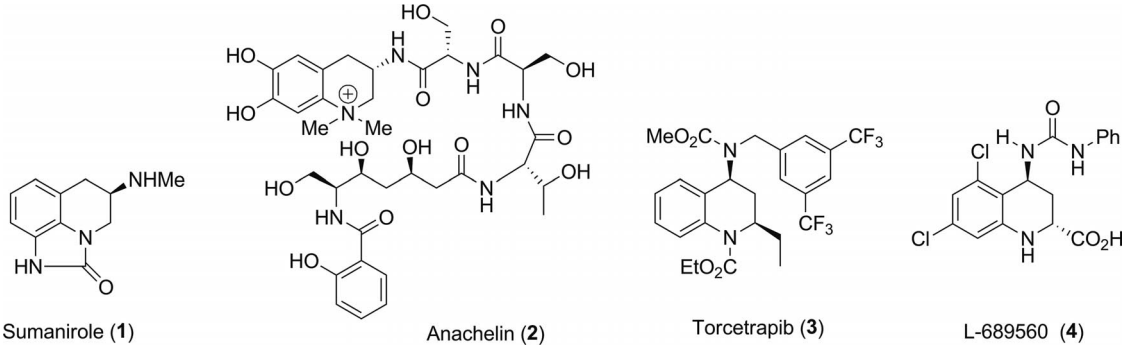

Figure 1. Biologically active 3- and 4-amino-substituted 1,2,3,4-THQs.

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cholesterolemia and prevent cardiovascular disease. Compound **4** is a strong NMDA (*N*-methyl-D-aspartate) receptor antagonist.[5]

Because of the relative paucity of 3- and 4-amino-substituted 1,2,3,4-THQs, it is by no means surprising that only few methods for the asymmetric preparation of this class of compounds have been reported so far. The installation of an NHR group at C-3 has been achieved by rhodium-catalyzed asymmetric reduction[6a] and by Sharpless oxidation[6a] or Sharpless dihydroxylation[6b] of a cinnamyl substrate followed by further manipulations to elaborate the 1,2,3,4-THQ skeleton. In the context of the synthesis of sumanirole,[7] an epoxide group, introduced through a Jacobsen's enantioselective epoxidation of a 1,2-dihydroquinoline, served as a precursor to an NHR group at C-3.[7b] Two examples of an enantioselective introduction of an NHR group at C-4 were recently disclosed, following an aza-Michael reaction[4a] and a three-component Povarov reaction,[4b] respectively. Because of the remarkable pharmacological activities demonstrated by sumanirole (**1**), we are interested in achieving its synthesis.

Results and Discussions

At the onset of our work, chiral Reissert adduct **7**[8] was to be used as a possible starting point. We believed that the cyano group could control the stereochemistry of the double-bond epoxidation and then be reductively removed later in the synthesis, as such or in the form of a closely matched derivative (e.g., a carboxylic acid). Indeed, preliminary investigations showed that epoxidation of Reissert adducts *rac*-**8a**[9] and *rac*-**8b**[10] selectively led to single epoxides **9a** and **9b**, which could be further reduced to alcohols **10a** and **10b**, respectively. Epoxide **9a** could also be opened to produce 1,2-diol **11**, whose structure was firmly established by single-crystal X-ray diffraction analysis (Scheme 1 and Figure 2).[11–13] Additionally, ester **13**,[14] derived from **8a** through amide **12**,[15] afforded, under the action of *m*CPBA (*meta*-chloroperbenzoic acid), single epoxide **14**, which was subsequently opened through hydrogenolysis in methanol to give compound **15**.[16]

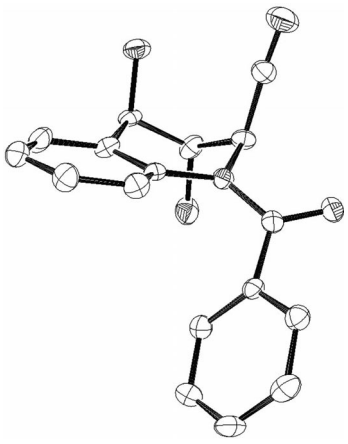
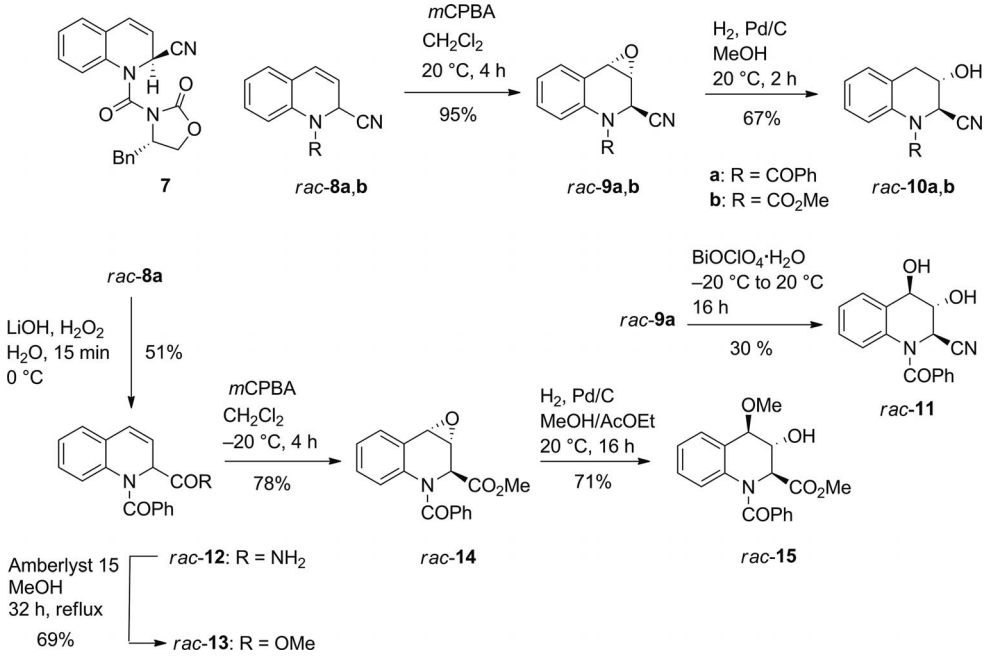
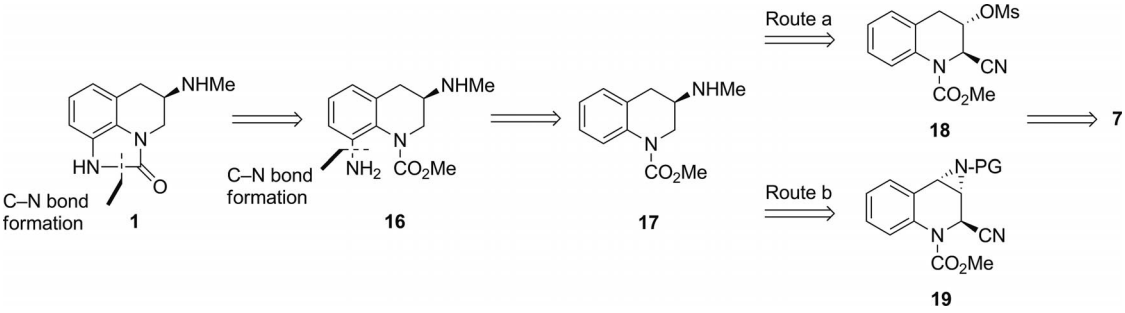


Figure 2. X-ray crystal structure of **11**.

On the basis of these preliminary observations, the retrosynthesis in Scheme 2 was first devised. Thus, sumanirole (**1**) could result from the cyclization of diaminocarbamate **16**, the latter being prepared from aminocarbamate **17**. At this juncture of the analysis, two routes could be followed. One featured the substitution of mesylate **18** with inversion of its configuration, and the other displayed the regioselective ring opening of aziridine **19**. Also, regardless of the



Scheme 1.



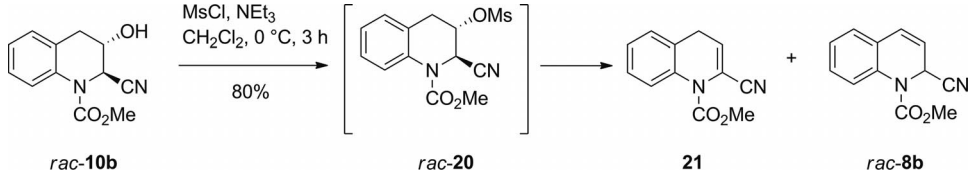
Scheme 2.

route chosen, access to **17** would require the removal of the CN group. Finally, mesylate **18** and aziridine **19** could each be derived from Reissert adduct **7**.

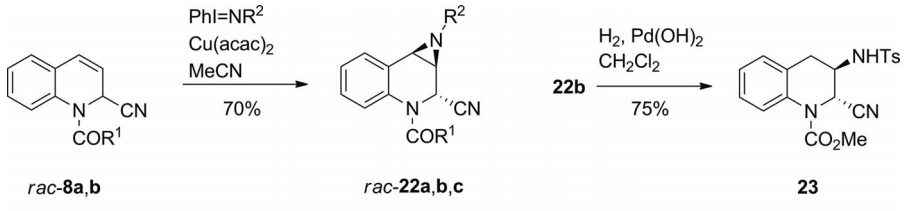
Alcohol *rac*-**10b** was initially chosen to test the feasibility of Route a. Treatment of **10b** with mesyl chloride in the presence of NEt_3 did not afford the expected mesylate **20**, but instead gave an inseparable mixture of dihydroquinolines **21** and **8b** as shown in Scheme 3.

The facile elimination of MsOH from mesylate **20** led us to abandon this route and envisage the formation of amine **17** through the selective ring opening of a protected aziridine (Scheme 2, Route b). Aziridination could be envisaged in one operation by a metal-catalyzed nitrogen atom transfer from a nitrene precursor. Using the conditions reported by Evans,[17] that is, using [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane as the nitrene precursor and $Cu(acac)_2$ as the metal catalyst, we were pleased to observe that Reissert adducts *rac*-**8a** and *rac*-**8b** were stereoselectively transformed into single aziridines **22a** and **22b**, respectively (Scheme 4). In a similar manner, we also prepared aziridine **22c** by action of the nitrene precursor PhI=N–Ses[18] on Reissert adduct **8b**. The *anti* disposition between the aziridine ring and the cyano substituent was confirmed by X-ray single-crystal analysis of aziridine **22a**.[19]

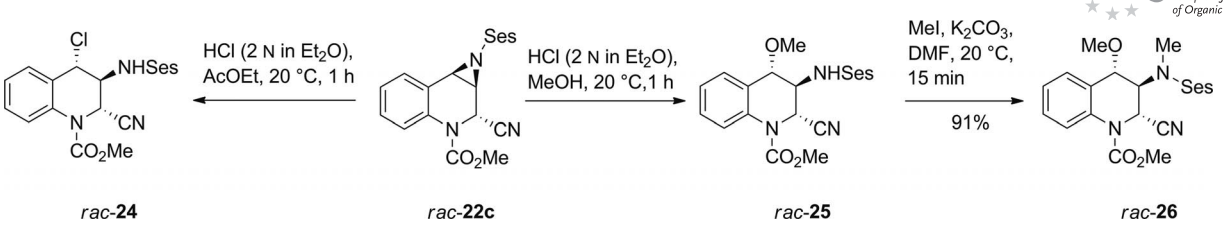
We next explored the conditions for the ring opening of aziridines **22b** and **22c** to give the corresponding monoprotected primary amines and the conditions for the subsequent transformation to install an NHMe substituent at C-3. The hydrogenolysis of aziridine **22b** was cleanly effected in the presence of palladium hydroxide to give amine **23** (Scheme 4). In contrast, under a variety of neutral conditions, aziridine **22c** was reluctant to undergo hydrogenolysis. However, **22c** was regioselectively opened in the presence of HCl to give either compound **24** or **25**, depending on the nature of the solvent (Scheme 5). Amine **25** also easily underwent *N*-methylation to give **26**.



Scheme 3.



Scheme 4.

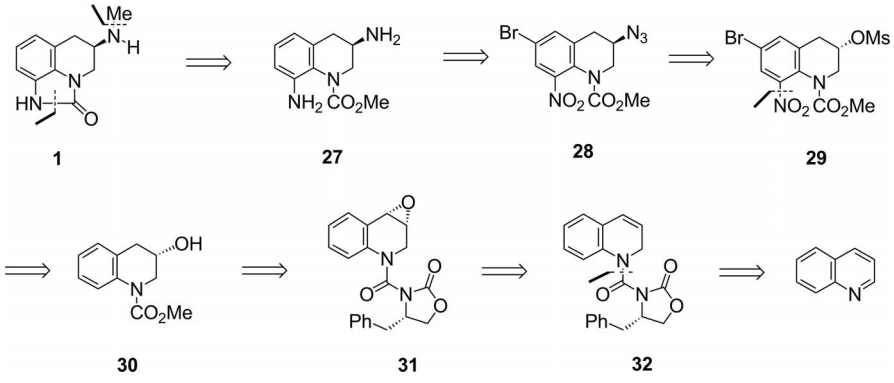


Scheme 5.

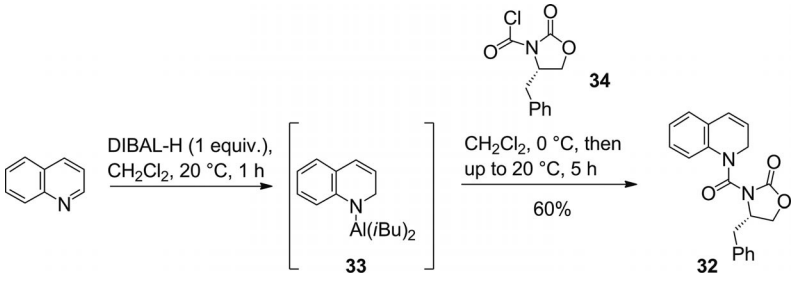
Although these exploratory studies were rather encouraging, we experienced failure when we tried to deprotect amines **23** and **26**, as all of the processes were clearly incompatible with the presence of the cyano group. Moreover, and for no obvious reasons, we observed that chiral Reissert adduct **7**, in contrast to *rac*-**8a** and *rac*-**8b**, failed to react with PhI=NTs/Cu(acac)$_2$. Finally, these setbacks led us to abandon the Reissert adduct based strategy and consider another route to sumanirole.

Thus, we were interested to discover if the epoxidation of chiral 1,2-dihydroquinoline **32** could be achieved with reasonable diastereoselectivity, despite the fact that the location of the chiral auxiliary in **32** is remote to the electrophilic C-3–C-4 double bond. If so, the resulting epoxide would be a useful intermediate for the synthesis of sumanirole. Anticipating a good result, a new strategy to reach (*R*)-**1** was then devised (Scheme 6).

Retrosynthetically, it was envisaged that (*R*)-**1** could be derived from diamine **27**, which in turn could be obtained through the reduction of an appropriately functionalized tetrahydroquinoline such as **28**, which could be derived from mesylate **29**. Access to **29** could be devised from alcohol **30**, which could be obtained from **31** by a regioselective opening of the epoxide ring and removal of the oxazolidinone moiety. Finally, the preparation of **31** could be envisaged through a diastereoselective epoxidation of chiral 1,2-dihydroquinoline **32**, prepared from quinoline.[20] Following this strategy, the preparation of the 1,2-dihydroquinoline **32** was first considered. Inspired by an early work of Minter and Slatter,[21] who reported the 1,2-reduction of quinoline along with subsequent trapping of the aminoalane intermediate by using a large excess amount of methyl chloroformate, quinoline was first treated with 1 equiv. of DIBAL-H (diisobutylaluminum hydride) for 1 h. Then, the resulting red solution of aminoalane **33** was added by syringe to a solution of chiral carbamoyl chloride **34**[22] in dichloromethane maintained at 0 °C. The best result was obtained when **34** was used as the limiting reagent (0.5 equiv.). In that case, the connection of the (*S*)-4-benzyl-2-oxooxazolidin-3-carbonyl and 1,2-dihydroquinoline fragments to give **32** was achieved in approximately 60% yield (Scheme 7).



Scheme 6.

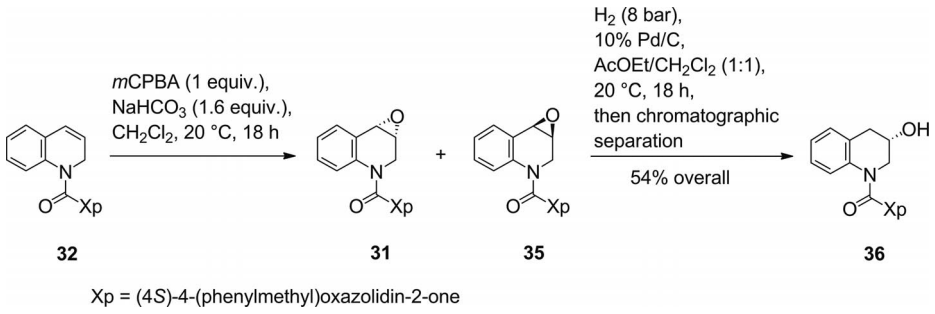


Scheme 7.

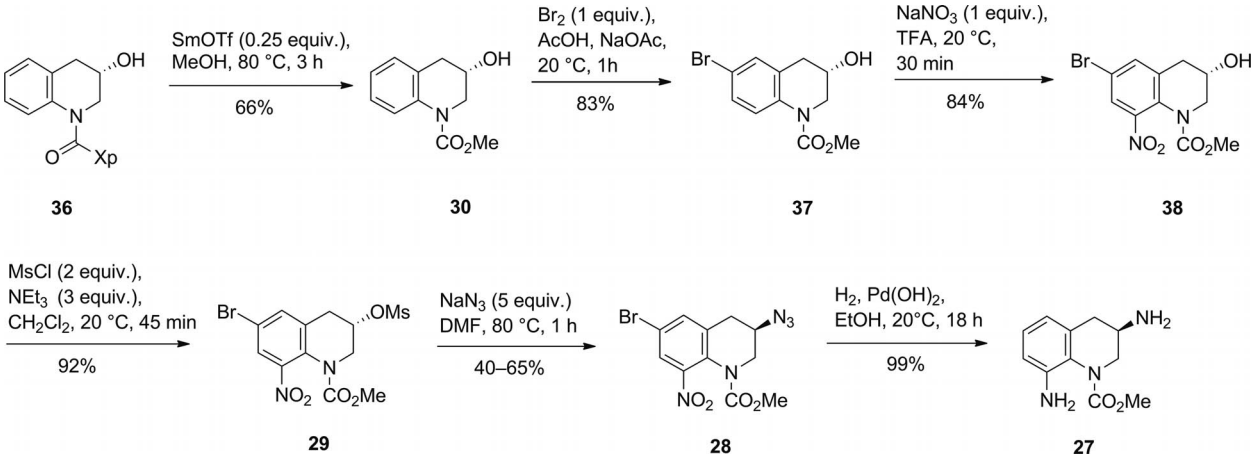
With the 1,2-dihydroquinoline **32** in hand, the key epoxidation reaction could now be examined. We were pleased to observe that the treatment of **32** with 1 equiv. of *m*CPBA led to a mixture of diastereomeric epoxides **31** and **35** in a ratio as high as 9:1 (Scheme 8). The addition of sodium hydrogen carbonate as a buffering agent was crucial to trap the *meta*-chlorobenzoic acid formed during the reaction, thereby avoiding its subsequent addition to the epoxide products. After chromatographic separation, the stereochemistry of the major epoxide **31** was fully ascertained by X-ray single-crystal diffraction.[20]

However, from a practical point of view, we found it preferable to first hydrogenate the epoxide mixture and subsequently separate the resulting mixture of alcohols. Following this protocol, alcohol **36** was isolated in 54% yield from 1,2-dihydroquinoline **32** (Scheme 8). At this juncture, we decided to perform the OH → NHMe transformation at a later stage in the synthesis and, instead, to concentrate first on the construction of the imidazolone ring. The direct installation of an amino group at C-8 through nitration was unrealistic, because the most nucleophilic center for the SEAr (electrophilic aromatic substitution) reaction of **36** would be C-6. It appeared necessary to temporarily protect this carbon atom, and a bromination/nitration sequence[23] was envisaged. Before applying this protocol, the chiral auxiliary in **36** was removed by treatment with samarium triflate in methanol[8] to give 1,2-dihydroquinoline **30**. The bromination of **30** proceeded well to give the expected 6-bromo derivative **37**, which was then submitted to the action of HNO_3 in TFA (trifluoroacetic acid) to afford the 6-bromo-8-nitro-1,2-dihydroquinoline **38** in about 70% yield over the two steps. At this stage, we suspended the imidazolone ring construction and returned to the installation of the NHMe group at C-3. Alcohol **38** was treated with mesyl chloride to give mesylate **29**, which was then transformed into azido compound **28** through the action of NaN_3 in DMF (*N*,*N*-dimethylformamide). At this point, our expectation was that reduction of both the azido and nitro groups as well as the hydrogenolysis of the C–Br bond would be effected in a single chemical operation. To our delight, the hydrogenation of **28** in the presence of Pearlmann's catalyst delivered diamino compound **27** in almost quantitative yield (Scheme 9).

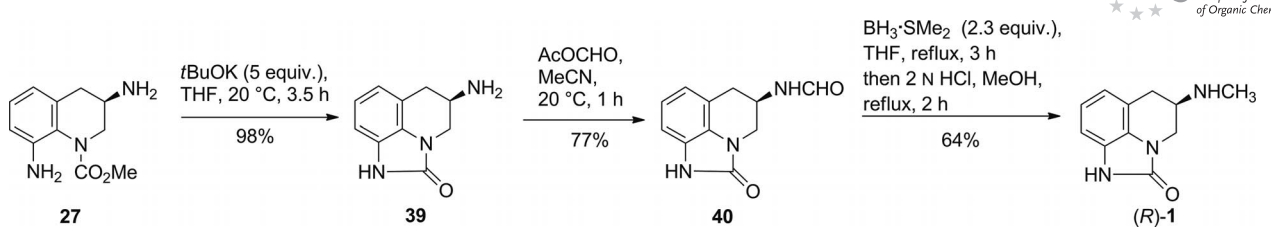
The transformation of **27** into sumanirole could then been achieved in three additional steps. The final construction of the imidazolone ring was achieved by treatment of **27** with an excess amount of *t*BuOK in THF (tetrahydrofuran). The resulting amine **39** was first transformed into its formamide **40**, which was then reduced with the $BH_3{\cdot}SMe_2$ complex to afford sumanirole [(*R*)-**1**], isolated as its hydrochloride (Scheme 10).



Scheme 8.



Scheme 9.



Scheme 10.

Conclusions

We have achieved the synthesis of sumanirole in twelve steps starting from quinoline. A key feature of our synthesis is the diastereoselective epoxidation of the C-3–C-4 double bond in 1,2-dihydroquinoline **32**, in spite of the fact that the chiral *N*-acyloxazolidinone auxiliary is remotely situated. Another remarkable feature is the concomitant transformation of three different groups under hydrogenation conditions. Recent studies in our laboratory have shown that other electrophilic additions to the C-3–C-4 double bond of **32** could be accomplished diastereoselectively. On the basis of experimental work and theoretical calculations, an explanation also emerged for the stereochemical preference. The results of these studies will be reported in a near future.

Experimental Section

(*S*)-4-Benzyl-3-(1,2-dihydroquinoline-1-carbonyl)oxazolidin-2-one (32): A solution of DIBAL-H (1 M solution in hexane, 13.6 mL, 13.6 mmol) was added dropwise to a solution of quinoline (1.6 mL, 14 mmol) in CH_2Cl_2 (18 mL) at 0 °C under argon. The stirring was continued at 0 °C for 1 h, and then the red solution was cannulated into a solution of carbamoyl chloride **34** (1.63 g, 6.8 mmol) in CH_2Cl_2 (2 mL) that was precooled to 0 °C. The resulting solution was stirred for 4 h, as the temperature was raised progressively to 20 °C. The reaction mixture was then cannulated into water (150 mL) at 0–5 °C. The resulting emulsion remained, as stirring was continued for 30 min, and then the mixture was acidified to pH = 4 with HCl (4 N solution). After phase separation, the aqueous phase was extracted with dichloromethane (4 × 60 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The resulting crude oil was subjected to flash column chromatography (toluene/petroleum ether/diethyl ether, 2:1:1; R_f = 0.26) to give compound **32** (1.39 g, 61%, calculation based on carbamoyl chloride **34**) as a clear yellow oil. $[a]_D^{20}$ = +7.7 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.40 (m, 9 H), 6.59 (dd, *J* = 9.6, 2.4 Hz, 1 H), 5.99–6.04 (m, 1 H), 4.73–4.78 (m, 1 H), 4.40 (dd, *J* = 17.0, 5.5 Hz, 1 H), 4.08–4.31 (m, 3 H), 2.92 and 3.26 (ABX system, *J* = 13.5, 8.7, 3.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 152.4, 136.0, 134.9, 129.5 (2 C), 129.2, 129.0 (2 C), 128.5, 128.3, 127.5, 126.7, 126.4, 125.5, 122.9, 67.0, 56.5, 45.9, 38.1 ppm. IR (KBr): $\tilde{\nu}$ = 1722, 1685, 1601–1454, 1090, 1060 cm^{-1}. MS (EI): *m*/*z* (%) = 334 (<1) $[M]^{+\cdot}$, 130 (100), 91 (19). HRMS (EI): calcd. for $C_{20}H_{18}N_2O_3$ $[M]^+$ 334.1317; found 334.1313.

(*S*)-4-Benzyl-3-[(1a*R*,7b*S*)-1a,2,3,7b-tetrahydrooxireno[2,3-*c*]-quinoline-3-carbonyl]oxazolidine-2-one (31): To a solution of the 1,2-dihydroquinoline **32** (1.6 g, 4.78 mmol) in CH_2Cl_2 (250 mL) at 20 °C were successively added sodium hydrogen carbonate (0.644 g, 6.22 mmol) and *m*CPBA (70–75% pure, 1.5 g, 6.22 mmol). The reaction mixture was stirred at 20 °C for 18 h under a continuous flow of argon and then washed with saturated aqueous sodium hydrogen carbonate (250 mL). After phase separation, the aqueous phase was extracted with dichloromethane (3 × 160 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give a white powder consisting of a mixture of the two diastereomeric epoxides **31** and **35** in a 9:1 ratio. The major diastereomer **31** was isolated in pure form, after the mixture was subjected to silica gel column chromatography (CH_2Cl_2/AcOEt, 9:1; R_f = 0.33); m.p. 204–206 °C. $[a]_D^{20}$ = +54.2 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.53 (m, 9 H), 4.57–4.75 (m, 1 H), 4.13 and 4.29 (ABX system, *J* = 9.0, 8.8, 8.4 Hz, 2 H), 3.98 (d, *J* = 4.2 Hz, 1 H), 3.90–3.92 (m, 1 H), 3.55 and 4.38 (AB system, *J* = 14.4 Hz, 2 H), 2.93 and 3.16 (ABX system, *J* = 13.8, 8.4, 3.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9 (2 C), 136.3, 134.7, 129.8 (2 C), 129.3, 129.0 (2 C), 127.4, 126.4, 125.9, 124.9, 66.7, 58.2, 56.4, 50.9, 44.0, 36.9 ppm. IR (KBr): $\tilde{\nu}$ = 1774, 1675, 1600–1438, 1118, 1066 cm^{-1}. MS (EI): *m*/*z* (%) = 350 (7) $[M]^{+\cdot}$, 322 (100), 174 (8). HRMS (EI): calcd. for $C_{20}H_{18}N_2O_4$ 350.1267; found 350.1266.

(*S*)-4-Benzyl-3-[(*S*)-3-hydroxy-1,2,3,4-tetrahydroquinoline-1-carbonyl]oxazolidin-2-one (36): Pd/C (10%, 0.668 g) was added to a solution of crude epoxides **31** and **35** (1.7 g) in a mixture of CH_2Cl_2/AcOEt (1:1). The mixture was stirred under hydrogen (8 bar) for 18 h and then filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2/AcOEt (1:1), and the filtrate was concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (AcOEt/petroleum ether, 1:1; R_f = 0.39) to give alcohol **36** (0.900 g, 54%) as white crystals; m.p. 137–138 °C. $[a]_D^{20}$ = –170.1 (*c* = 0.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00, 7.40 (m, 9 H), 4.80 (m, 1 H), 4.28 (m, 1 H), 4.11 and 4.24 (ABX system, *J* = 8.4, 8.4, 7.5 Hz, 2 H), 3.38 and 4.41 (ABX system, *J* = 12.6, <1, <1 Hz, 2 H), 2.99 and 3.15 (ABX system, *J* = 18.0, 5.4, <1 Hz, 2 H), 2.85 and 3.60 (ABX system, *J* = 12.9, 10.2, 3.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1, 152.9, 138.0, 133.9 (2 C), 129.4, 128.1 (2 C), 128.0, 126.5, 125.2, 124.2, 120.3, 67.2, 62.9, 55.2, 50.6, 37.0, 34.7 ppm. IR (film): $\tilde{\nu}$ = 3452, 1772, 1683, 1604, 1583, 1493, 1455, 1220, 1074 cm^{-1}. MS (EI): *m*/*z* (%) = 323 (9) $[M]^{+\cdot}$, 132 (38), 130 (38), 118 (20), 117 (16), 91 (100). HRMS (EI): calcd. for $C_{20}H_{20}N_2O_4$ 352.1423; found 352.1427.

Methyl (3*S*)-3-Hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate (30): Samarium triflate (0.569 g, 0.95 mmol) was added to a solution of alcohol **31** (1.34 g, 3.80 mmol) in anhydrous methanol. The mixture was stirred at 80 °C for 2 h and then filtered through a pad of silica. The filter cake was rinsed with AcOEt, and the filtrate was concentrated in vacuo. The resulting crude product was purified by

silica gel column chromatography (petroleum ether/diethyl ether, 1:4; R_f = 0.5) to give alcohol **30** as a clear yellow oil. $[\alpha]_D^{20}$ = +6.0 (c = 0.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.2 Hz, 1 H), 7.18 (t, J = 8.2 Hz, 1 H), 7.11 (d, J = 8.2 Hz, 1 H), 7.06 (t, J = 8.2 Hz, 1 H), 4.31 (m, 1 H), 3.82 (d, J = 4.6 Hz, 2 H), 3.80 (s, 3 H), 2.82 and 3.10 (ABX system, J = 16.3, 5.2, 5.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 137.5, 129.5, 126.7, 126.3, 124.3, 123.8, 65.0, 53.1, 50.5, 36.0 ppm. IR (film): $\tilde{\nu}$ = 3429, 1699, 1600, 1582, 1463, 1441 cm^{-1}. MS (EI): m/z (%) = 207 (100) $[M]^{+\cdot}$, 178 (20), 147 (36), 130 (41), 118 (59), 91 (57), 77 (22). HRMS (EI): calcd. for $C_{11}H_{13}NO_3$ 207.0895; found 207.0894. Note: (4*S*)-4-benzyloxazolidin-2-one was recovered with a yield of 66%.

Methyl (3*S*)-6-Bromo-3-hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate (37): To a solution of alcohol **30** (0.228 g, 1.39 mmol) in acetic acid were successively added anhydrous AcONa (0.214 g, 1.88 mmol) and Br_2 (0.071 mL, 1.39 mmol). The mixture was stirred at 20 °C for 1 h and then quenched with water (30 mL). The resulting solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in cyclohexane, and the solution was concentrated in vacuo to azeotropically remove the traces of AcOH. The crude bromo alcohol **37** (orange, amorphous solid) was used in the next step without further purification. $[\alpha]_D^{20}$ = –11.0 (c = 0.33, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.7 Hz, 1 H), 7.24–7.30 (m, 2 H), 4.28 (m, 1 H), 3.79 (s, 3 H), 3.71–3.88 (m, 2 H), 2.78 and 3.05 (ABX system, J = 16.8, 5.1, 2.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 136.7, 132.0, 129.6, 128.8, 125.4, 117.1, 64.4, 53.3, 50.32, 35.7 ppm. IR (KBr): $\tilde{\nu}$ = 3413, 1709, 1600, 1580, 1486, 1442, 817 cm^{-1}. MS (EI): m/z (%) = 285/287 (100) $[M]^{+\cdot}$, 117 (58), 90 (20). HRMS (EI): calcd. for $C_{11}H_{12}BrNO_3$ 285.0001; found 285.0001.

Methyl (3*S*)-6-Bromo-3-hydroxy-8-nitro-3,4-dihydroquinoline-1(2*H*)-carboxylate (38): To a solution of sodium nitrate (0.041 g, 0.48 mmol) in trifluoroacetic acid (2 mL) was added bromo alcohol **37**. The resulting solution was stirred at 20 °C for 30 min and then concentrated in vacuo. AcOEt (20 mL) and water (10 mL) were then added to the residue. After separation, the organic layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (10 mL), NaOH (1 M solution, 10 mL), and water (10 mL), dried with $MgSO_4$, and then concentrated in vacuo. The crude product was purified by silica gel column chromatography (CH_2Cl_2/AcOEt, 3:2; R_f = 0.5) to give nitro compound **38** (0.132, 84%) as a white solid; m.p. 123 °C. $[\alpha]_D^{20}$ = +25.4 (c = 0.41, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 7.64 (d, J = 2.4 Hz, 1 H), 6.84 (d, J = 2.4 Hz, 1 H), 3.59, (m, 1 H), 3.38 (s, 3 H), 3.30 (m, 2 H), 2.16 and 2.23 (ABX system, J = 16.4, 5.2, 4.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 154.9, 145.1, 136.0, 134.0, 131.3, 126.1, 117.3, 65.1, 53.1, 50.7, 35.6 ppm. IR (film): $\tilde{\nu}$ = 3441, 1700, 1601, 1528, 1471, 1452, 1441, 1370 cm^{-1}. MS (EI): m/z (%) = 330/332 (8) $[M]^{+\cdot}$, 284/286 (66), 201 (48), 173 (51), 117 (100). HRMS (EI): calcd. for $C_{11}H_{11}BrN_2O_5$ 329.9851; found 329.9854.

Methyl (3*S*)-6-Bromo-3-[(methylsulfonyl)oxy]-8-nitro-3,4-dihydroquinoline-1(2*H*)-carboxylate (29): To a stirred solution of alcohol **38** (0.282, 0.85 mmol) in anhydrous CH_2Cl_2 (16 mL) kept at 20 °C under nitrogen (16 mL) were successively added freshly distilled NEt_3 (0.360 mL, 2.56 mmol) and mesyl chloride (0.132 mL, 1.71 mmol). After stirring was continued for 45 min, CH_2Cl_2 (90 mL) was added to the reaction mixture, which was then washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (CH_2Cl_2/AcOEt, 9:1; R_f = 0.46) to give mesylate **29** (0.320 g, 92%) as a yellow solid; m.p. 160 °C. $[\alpha]_D^{20}$ = +34.0 (c = 0.20, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 7.62 (s, 1 H), 4.74 (s, 1 H), 4.66 (m, 1 H), 3.90 (br. s, 1 H), 3.36 (br. s, 2 H), 2.20 and 2.47 (ABX system, J = 12.6, 3.3, 3.0 Hz, 2 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 154.1, 145.0, 135.8, 132.0, 131.0, 126.6, 117.7, 73.1, 53.1, 48.1, 38.2, 33.5 ppm. IR (KBr): $\tilde{\nu}$ = 1721, 1601, 1528, 1471, 1460, 1452, 1310–1350, 1369, 1170 cm^{-1}. MS (EI): m/z (%) = 408/410 (13) $[M]^{+\cdot}$, 362/364 (88), 207/209 (57). HRMS (EI): calcd. for $C_{12}H_{13}BrN_2O_7S$ 407.9627; found 407.9630.

Methyl (3*R*)-3-Azido-6-bromo-8-nitro-3,4-dihydroquinoline-1(2*H*)-carboxylate (28): To a solution of mesylate **29** (0.250 g, 0. 61 mmol) in anhydrous DMF (11 mL) kept at 20 °C under nitrogen was added sodium azide (0.199 g, 3.06 mmol). The resulting solution was stirred at 20 °C for 1 h and then quenched with water (50 mL). After separation, the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried with $MgSO_4$ and then concentrated in vacuo. The crude product was purified by silica gel column chromatography (petroleum ether then petroleum ether/Et_2O, 3:2; R_f = 0.34) to give azide **28** (0.140 g, 65%) as an orange oil. $[\alpha]_D^{20}$ = +58.4 (c = 0.51, $CHCl_3$). ^1H NM R (400 MHz, C_6D_6): δ = 7.63 (s, 1 H), 6.73 (s, 1 H), 3.50 (br. s, 2 H), 3.38 (s, 3 H), 3.04 (m, 1 H), 2.02 and 2.08 (ABX system, J = 17.0, 5.2, 5.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 154.6, 145.6, 136.0, 133.2, 131.6, 127.0, 117.8, 56.0, 53.6, 48.1, 32.9 ppm. IR (KBr): $\tilde{\nu}$ = 2106, 1717, 1539, 1363 cm^{-1}. MS (EI): m/z (%) = 355/357 (31) $[M]^{+\cdot}$, 309/311 (42), 209/211 (35), 89/90 (100). HRMS (EI): calcd. for $C_{11}H_{10}BrN_5O_4$ 354.9916; found 354.9923.

Methyl (3*R*)-3,8-Diamino-3,4-dihydroquinoline-1(2*H*)-carboxylate (27): $Pd(OH)_2$/C (20%, 0.025 g) was added to a solution of azide **28** (0.2 g, 1. 52 mmol) in ethanol (13 mL), and the resulting mixture was stirred under hydrogen (1 bar) for 18 h. The reaction mixture was filtered through a pad of Celite, and the filter cake was rinsed with ethanol. The ethanolic filtrate was concentrated in vacuo, and the crude residue was dissolved in saturated aqueous sodium hydrogen carbonate (5 mL). The solution was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were dried with Na_2SO_4 and then concentrated in vacuo. The crude diamino ester derivative **27** (0.1 g, 99%, brown oil) was used in the next step without further purification. $[\alpha]_D^{20}$ = +25.1 (c = 0.31, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 6.88 (t, J = 7.2 Hz, 1 H), 6.45 (d, J = 7.2 Hz, 1 H), 6.36 (d, J = 7.2 Hz, 1 H), 3.72 (br. s, 2 H), 3.47 (s, 3 H), 2.99 (m, 1 H), 2.13 and 2.65 (ABX system, J = 15.8, 7.2, 6.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 156.0, 143.0, 133.6, 128.0, 127.2, 119.6, 116.5, 54.1, 53.2, 49.3, 38.5 ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3361, 1692 cm^{-1}. MS (EI): m/z (%) = 221 (100) $[M]^{+\cdot}$, 204 (24), 133 (32). HRMS (EI): calcd. for $C_{11}H_{15}N_3O_2$ 221.1164; found 221.1167.

(5*R*)-5-Amino-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-1(2*H*)-one (39): To a solution of the crude diamino ester **27** (0.250 g, 1.13 mmol) in dry THF (3 mL) was added a solution of *t*BuOK [20% (w/w) in THF, 3.4 mL, 5.65 mmol]. After the reaction mixture was stirred at 20 °C for 3.5 h, water and AcOEt were added. After separation, the aqueous phase was extracted with AcOEt (5 × 20 mL). The combined organic layers were dried with Na_2SO_4 and then concentrated in vacuo. The crude amino derivative **39** (0.210 g, 98%, brown powder) was used in the next step without further purification; m.p. 153 °C. $[\alpha]_D^{20}$ = –7.1 (c = 0.16, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO): δ = 10.6 (s, 1 H), 6.88 (dd, J = 8.9, 6.8 Hz, 1 H), 6.79 (d, J = 8.9 Hz, 1 H), 6.77 (d, J = 6.8 Hz, 1 H), 3.86 (m, 1 H), 3.52 (br. s, 2 H), 2.91 (dd, J = 15.9, 3.3 Hz, 1 H), 2.50 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ =

135.6, 127.1, 126.3, 120.5, 119.0, 117.7, 106.3, 45.6 (2 C), 29.3 ppm. IR (KBr): $\tilde{\nu}$ = 3300, 1684 cm^{-1}. MS (EI): *m*/*z* (%) = 189 (100) $[M]^{+\cdot}$, 171 (35), 147 (30). HRMS (EI): calcd. for $C_{10}H_{11}N_3O$ 189.0902; found 189.0903.

(5*R*)-5-(Formylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-1(2*H*)-one (40): To a solution of amine **39** (0.170 g, 0.9 mmol) in acetonitrile (0.9 mL) was added a preformed mixture of Ac_2O/HCO_2H (1:1, 0.28 mL) and Ac_2O (0.570 mL). The resulting solution was stirred under argon at 20 °C for 2 h and then concentrated in vacuo. To the residue was added MeOH (15 mL), and the solution was stirred at 20 °C for 1 h. After concentration in vacuo, the crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 95:5; R_f = 0.12) to give formamide **40** (0.150 g, 77%) as an orange solid; m.p. 215 °C. $[\alpha]_D^{20}$ = –153 (*c* = 0.14, $CHCl_3$). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 10.74 (s, 1 H), 8.33 (d, *J* = 6.0 Hz, 1 H), 8.02 (s, 1 H), 6.96 (dd, *J* = 9.0, 8.8 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 6.79 (d, *J* = 9.0 Hz, 1 H), 4.46 (m, 1 H), 3.70 and 3.90 (ABX system, *J* = 12.0, 6.0, 3.0 Hz, 2 H), 2.86 and 3.07 (ABX system, *J* = 18.0, 6.0, 3.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 160.9, 153.7, 126.9, 126.5, 120.7, 119.3, 116.1, 106.6, 42.0, 41.4, 29.1 ppm. IR (KBr): $\tilde{\nu}$ = 1576–1727 cm^{-1}. MS (EI): *m*/*z* (%) = 217 (16) $[M]^{+\cdot}$, 171 (100). HRMS (EI): calcd. for $C_{11}H_{11}N_3O_2$ 217.0851; found 217.0859.

(5*R*)-5-(Methylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-1(2*H*)-one [(*R*)-1]: To a stirred solution of formamide **40** (0.130 g, 0.6 mmol) in anhydrous THF (0.330 mL) was added dropwise a solution of BH_3·Me_2S complex (2 M solution in THF, 0.670 mL, 1.4 mmol). The stirring was continued at 20 °C under argon for 3 h. After concentration of the reaction mixture, a solution of HCl (2 N solution) in Et_2O (2.5 mL) and MeOH (2 mL) was added. The resulting solution was heated at reflux for 2 h. After cooling to 20 °C, the solution was concentrated in vacuo. The solid residue was triturated with a mixture of MeOH/Et_2O (1:1) and then filtered to give (*R*)-**1**·HCl as a brown solid (0.77 g, 63%). M.p. 297 °C (cf. 308 °C,[24a] >310 °C[24b]). $[\alpha]_D^{20}$ = –33.5 (*c* = 0.1, MeOH) (cf. –35.1,[24a] –30.3[24b]). ^{1}H NMR (300 MHz, D_2O): δ = 7.05 (dd, *J* = 8.0 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 3.99 (m, 1 H), 3.96 and 4.17 (ABX system, *J* = 13.3, 2.9, <1 Hz, 2 H), 3.13 and 3.27 (ABX system, *J* = 17.3, 2.8, 2.5 Hz, 2 H), 2.70 (s, 3 H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 155.0, 126.0 (2 C), 122.7, 120.5, 113.9, 108.7, 52.2, 39.3, 31.0, 25.9 ppm. IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}. MS (EI): *m*/*z* (%) = 203 (100) $[M]^{+\cdot}$, 171 (28), 162 (30). HRMS (EI): calcd. for $C_{11}H_{13}N_3O$ 203.1059; found 203.1062.

Supporting Information (see footnote on the first page of this article): General experimental methods, experimental procedures, analytical data for compounds **8a**, **9a**, **9b**, **10a**, **10b**, **11**–**15**, **22a**–**22c**, and **23**–**26**, significant ^{1}H and ^{13}C NMR spectra of all new compounds, and crystallographic data of compound **11**.

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