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Enantioselective Synthesis of Benzyl (1*S*,2*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-2-(hydroxymethyl)-cyclohexylcarbamate Using an Iodolactamization As the Key Step

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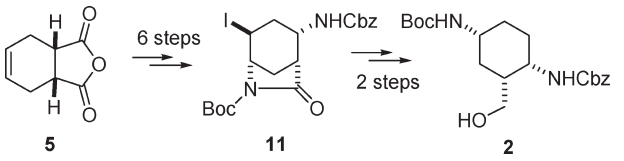

An efficient enantioselective synthesis of benzyl (1*S*,2*R*,4*R*)-4-(*tert*-butoxycarbonylamino)-2-(hydroxymethyl)cyclohexylcarbamate **2**, an essential intermediate for a series of potent CCR2 antagonists, is described. The key step in the sequence is an iodolactamization to yield the highly functionalized (1*R*,2*S*,4*S*,5*S*)-*tert*-butyl 2-(benzyloxycarbonylamino)-4-iodo-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate **11**. An examination of the reaction mechanism within the 2-step iodolactamization sequence led to the discovery of a single-pot transformation of increased efficiency.

Substituted cyclohexanes are a fundamental building block in organic chemistry. Many natural products and medicinally important compounds contain substituted cyclohexanes, including FK-506,[1] wailupemycin A,[2] and Factor Xa inhibitors.[3] Recently,[4] we discovered that 1,2,4-trisubstituted cyclohexanes are an essential scaffold for a series of potent CCR2 antagonists **1**. In order to optimize the properties of these antagonists, we required a scalable, entantioselective synthesis of the core intermediate, benzyl (1*S*,2*R*,4*R*)-4-(*tert*-butoxycarbonylamino)-2-(hydroxymethyl)-cyclohexylcarbamate **2**. In this paper, we describe the full details of our synthesis of **2**.[5] To our knowledge, a synthesis of **2** has not appeared, although some work has been published on related diastereomers of 1,4-diamino-2-(carboxylate)cyclohexanes that was not suitable for our needs.[6] As shown in Scheme 1, we envisioned that **2** would be available from the cyclic compound **3**, which in turn could be synthesized from an enantiomerically enriched monoacid **4**. The enantiomer we needed in **4** was opposite that obtained via a pig liver esterase cleavage of a diester.[7]

Hence, we initiated the synthesis of **2** with an asymmetric methanolysis of the inexpensive 1,2,3,6-tetrahydrophthalic anhydride **5**, as described by Bolm et al.,[8] to give the monoacid **6** in 86−92% yield and 93% ee[9] (Scheme 2). The free carboxylate of **6** was then transformed via a Curtius reaction to carbamate **7**.[10] Saponification of the ester gave carboxylate **8**,[11] which was converted to amide **9**. We were unable to perform a lactamization directly[13] on amide **9**, and so we explored making the amide NH more acidic to promote lactamization.[14] After some experimentation, we found that treatment of amide **9** in a NMP/THF mixture with *n*-BuLi and Boc_2O[15] gave the acyl carbamate **10**. We were then able to utilize lactamization

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(9) Bolm and co-workers have reported[8a] the enantiopurity of **6** to be 93% ee for this process, and we have confirmed that our material meets this specification, using the 4-bromophenyl ester[8a] of **6** and HPLC conditions (AD column, 4.6 × 250 mm, 93% *n*-heptane/7% 2-propanol, 1 mL/min, 220 nm, $t_1 = 7.8$ (major), $t_2 = 8.6$ min (minor).
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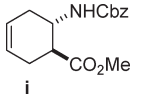
(11) We did not observe α-epimerization in the saponification of **7** to **8**. This was confirmed by converting carboxylate **8** back to ester **7** (via $TMSCHN_2$) and then examining the ^1H NMR. The *anti*-diastereomer **i** has been previously reported[12] to have a methyl ester resonance in the ^1H NMR at 3.64 ppm, and we did not observe this in our sample of **7** (resynthesized from **8**).



i

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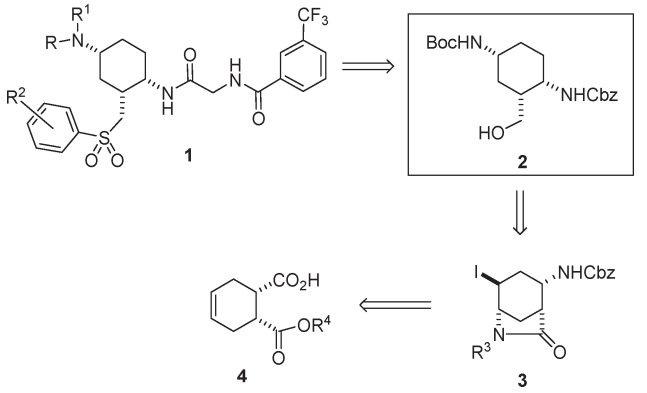
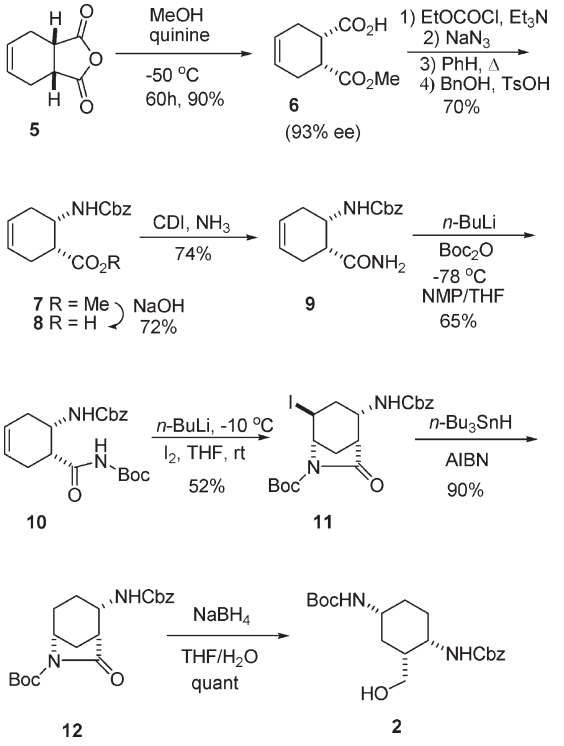
SCHEME 1. Retrosynthetic Analysis of 2

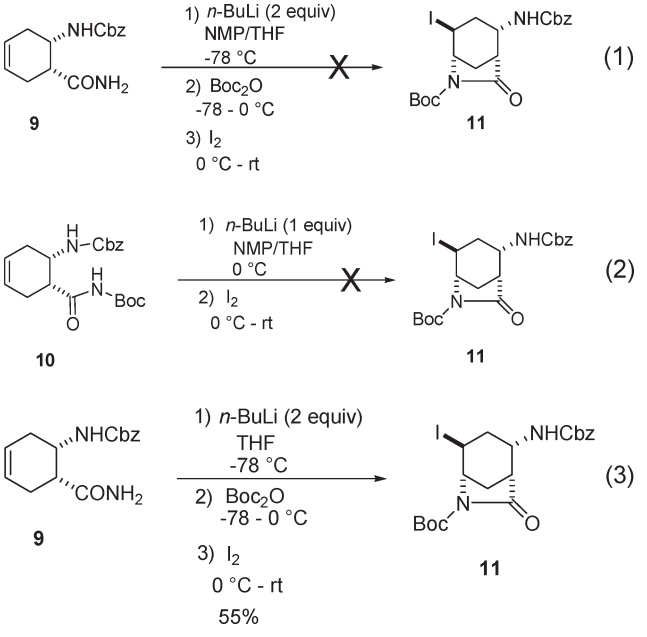


SCHEME 2. Enantioselective Synthesis of Trisubstituted Cyclohexane 2



conditions described by Taguchi et al.[14b] (*n*-BuLi and I_2) to afford the cyclized **11**.[16] Dehalogenation occurred smoothly with *n*-Bu_3SnH and AIBN to give **12**. The desired **2** was then produced by a reductive opening of **12** with $NaBH_4$ in a THF/H_2O (4/1) mixture. The addition of water to this reductive opening was critical for its success.

As shown in Scheme 2, the synthesis of **2** was accomplished in eight steps with an overall yield of 10% from **5**. However, when we examined the lactamization sequence, we hypothesized that the acylation of amide **9** and the subsequent iodocyclization to **11** could be more efficiently performed as a one-pot procedure. Based on the reaction mechanism, our hypothesis was that amide **9** could be dilithiated in situ to **13** and then quenched with 1 equiv of Boc_2O to give **14** (Scheme 3). With the acyl carbamate NH now very acidic, a proton transfer could give **15** in situ, which when exposed to iodine should undergo the cyclization to yield **11**. As shown in eq 1, when we attempted the one-pot procedure with racemic **9**,[17] we did not observe any of the desired *rac*-**11**. However, we noticed that the iodocyclization had never been run in the presence of NMP, which was necessary only for the solubility of amide **9** in the acylation step. To investigate this, we ran a control reaction using our normal lactamization conditions of **10**, but in the presence of NMP (eq 2). Surprisingly, the lactamization failed to occur in the presence of NMP. Hence, we returned to the one-pot concept and excluded NMP (eq 3). Treatment of **9** (noncrystalline material for solubility purposes) with 2 equiv of *n*-BuLi at low temperature followed by Boc_2O and then iodine gave the successful iodolactamization to *rac*-**11** in a single pot (eq 3). The one-pot process was more efficient as it proceeded in 55% yield as compared to a 34% yield for the two-step procedure.



In summary, we have described an efficient, enantioselective synthesis of benzyl (1*S*,2*R*,4*R*)-4-(*tert*-butoxycarbonylamino)-2-(hydroxymethyl)cyclohexylcarbamate **2**, which is an essential core for a series of potent CCR2 antagonists. The key step in the sequence was an iodolactamization to yield the highly functionalized **11**. An examination of the reaction mechanism within the two-step amide acylation/iodolactamization sequence led to the discovery of a single-pot transformation of increased efficiency.

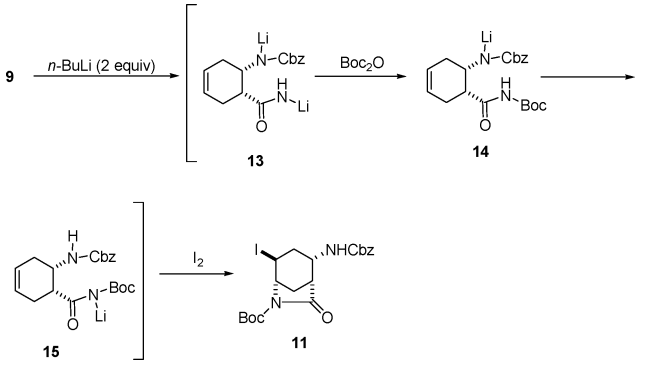
Experimental Section

(1*R*,2*S*,4*S*,5*S*)-*tert*-Butyl 2-(Benzyloxycarbonylamino)-4-iodo-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (11). The acyl carbamate **10** (2.6 g, 6.9 mmol) was dissolved in anhydrous THF (116 mL) and cooled in an ice/brine bath. After 15 min, *n*-BuLi (2.39 M, 2.9 mL, 6.9 mmol) was added dropwise. The resulting solution was stirred an additional 30 min before solid iodine (5.3 g,

(16) The enantiomeric integrity of compound **11** was confirmed to be 93% ee, using HPLC conditions (OJ column, 4.6×150 mm, 80% *n*-heptane/10% EtOH/10% MeOH and 0.1% diethylamine, 1 mL/min, 217 nm, $t_1 = 6.9$ (major), $t_2 = 8.4$ min (minor).

(17) All one-pot investigations were performed with racemic material out of convenience.

SCHEME 3. Proposed One-Pot Synthesis of 9 to 11



20.8 mmol) was added in a single portion. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 24 h. The iodine was quenched with 2 M aqueous $Na_2S_2O_3 \cdot 5H_2O$ solution (16 mL) to yield a pale yellow solution. A majority of the THF was removed by rotary evaporation prior to the addition of ethyl acetate (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water (2×45 mL) and brine (2×50 mL), dried (Na_2SO_4), filtered, and concentrated to a pale yellow solid. This solid was diluted with ether to make a slurry, and the solid material was collected by vacuum filtration. The product was repeatedly rinsed with cold ether and dried to give **11** (1.79 g, 3.6 mmol, 52%) as a white solid: mp 183.9, 194 °C, DSC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.20−5.03 (m, 3H), 4.62 (br m, 1H), 4.43 (br t, J = 4.3 Hz, 1H), 4.18 (m, 1H), 2.73 (br m, 1H), 2.62 (d, J = 12.5 Hz, 1H), 2.51 (dd, J = 16.0, 5.5 Hz, 1H), 2.34−2.25 (m, 1H), 2.14−2.02 (m, 1H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 155.6, 149.3, 136.4, 128.7, 128.4, 128.2, 84.2, 67.2, 60.5, 47.6, 46.0, 36.8, 31.5, 28.2, 21.2; $[\alpha]^{25}_D$ −69.6 (*c* 1.0, MeOH); IR (ATR) 3291, 2981, 1732, 1701, 1541, 1454, 1363, 1308, 1224, 1198 cm^{-1}; ESI MS *m*/*z* 401 $[C_{20}H_{25}IN_2O_5 - C_5H_8O_2 + H]^+$. Anal. Calcd for $C_{20}H_{25}IN_2O_5$: C, 48.01; H, 5.04; N, 5.60; I, 25.36. Found: C, 48.03; H, 4.79; N, 5.38; I, 25.27.

(1*R*,2*S*,5*R*)-*tert*-Butyl 2-(Benzyloxycarbonylamino)-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (12). A mixture of iodolactam **11** (38.2 g, 76.4 mmol) and 2,2′-azobisisobutyronitrile (626 mg, 3.8 mmol) in deoxygenated benzene (510 mL) was stirred under nitrogen as tri-*n*-butyltin hydride (24.4 g, 0.084 mol) was added in a single portion. The resulting mixture was slowly warmed to a gentle reflux, and this was stirred for 0.66 h. TLC at this time indicated the reaction was complete. Solvent was removed by rotary evaporation, and the residue was dried briefly under vacuum to yield a pasty solid. The solid was broken up, suspended in hexanes (450 mL), and stirred vigorously for 2 h. After being cooled in an ice−water bath for 0.25 h, the solid material was collected by vacuum filtration, rinsed with cold hexanes (3×150 mL), and dried under vacuum to afford **12** (26.2 g, 70.0 mmol, 91%) as a white solid. Recrystallization of a 200 mg sample from 10% ethyl acetate/hexanes afforded an analytical sample (168 mg, mp 96.9 °C, DSC): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 5H), 5.19 (d, J = 8.9 Hz, 1H) 5.14−4.95 (m, 2H), 4.30 (br t, J = 4.4 Hz, 1H), 3.97−3.81 (m, 1H), 2.68 (br d, J = 2.7 Hz, 1H), 2.33−1.99 (m, 3H), 1.52 (s, 9H), 1.71−1.10 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 155.5, 149.5, 136.3, 128.5, 128.0, 127.9, 83.0, 77.2, 66.7, 55.0, 48.5, 47.2, 33.8, 28.0, 26.7, 26.2; $[\alpha]^{25}_D$ −113.6 (*c* 1.03, MeOH); IR (ATR) 3320, 2978, 1736, 1698, 1530, 1450, 1367, 1315, 1237, 1216 cm^{-1}; ESI MS *m*/*z* 275 $[C_{20}H_{26}N_2O_5 - C_5H_8O_2 + H]^+$. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 63.97; H, 6.63; N, 7.37.

Benzyl (1*S*,2*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-2-(hydroxymethyl)cyclohexylcarbamate (2). To a solution of lactam **12** (10.5 g, 28 mmol) in THF (180 mL) and water (45 mL) was added sodium borohydride (5.3 g, 140 mmol) portionwise, and the mixture was stirred for 20 h at room temperature. The reaction was quenched by slow addition of satd NH_4Cl (200 mL), and the product was extracted with ethyl acetate (3×200 mL). The combined extracts were washed with brine, dried over sodium sulfate, and evaporated to give the desired alcohol **2** as a white solid (10.6 g, 100% yield). The material was pure enough for various transformations.

An analytical sample was obtained by recrystallization of the above solid with ethyl acetate and hexane: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.29−7.39 (m, 5H), 7.00 (d, J = 7.47 Hz, 1H), 6.53 (d, J = 7.03 Hz, 1 H), 5.02 (s, 2H), 4.38 (t, J = 5.27 Hz, 1H), 3.78 (d, J = 3.52 Hz, 1 H), 3.26−3.36 (m, 1H), 3.09−3.22 (m, 2H), 1.76 (d, J = 10.11 Hz, 1H), 1.60 (d, J = 10.55 Hz, 2H), 1.52 (d, J = 6.15 Hz, 1H), 1.43−1.32 (m, 1H), 1.37 (s, 9H), 1.06−1.23 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 154.7, 137.1, 128.3, 127.8, 77.3, 65.2, 62.6, 49.0, 46.0, 41.8, 29.8, 29.5, 28.3, 26.7; $[\alpha]^{25}_D$ +43.12 (*c* 0.517, MeOH); IR (KBr) 3374, 3265, 2942, 1705, 1666, 1562, 1454, 1389, 1271, 1177, 1113 cm^{-1}; high res MS calcd for $(M + Na)^+$ 401.20603, found 401.20540. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.26; H, 7.95; N, 7.33.

One-Pot Procedure: (1*R,2*S**,4*S**,5*S**)-*tert*-Butyl 2-(benzyloxycarbonylamino)-4-iodo-7-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (*rac*-11).** Racemic amide **9** (500 mg, 1.82 mmol) in THF (36 mL) was cooled to −70 °C (internal temperature) and stirred as *n*-BuLi (2 equiv, 3.64 mmol) was slowly added to keep the temperature ≤−65 °C. The resulting mixture was stirred at −70 °C for 30 min after which time a solution of di-*tert*-butyl dicarbonate (398 mg, 1.82 mmol) in tetrahydrofuran (1.5 mL) was slowly added to keep the temperature ≤−60 °C. After the mixture was stirred for 30 min at −70 °C, the flask was transferred to an ice−water bath and allowed to warm to 0 °C with stirring (15 min). Solid iodine (1.39 g, 5.47 mmol) was then added in a single portion. After 15 min, the bath was removed, and the resulting mixture was allowed to warm to room temperature and stirred for 14 h. Iodine was quenched with aqueous sodium thiosulfate (9.1 mmol in 15 mL water), and the mixture was extracted with ethyl acetate (2×50 mL). The extracts were combined, washed with water (2×30 mL) and brine (2×30 mL), dried (Na_2SO_4), filtered, and concentrated to a pale yellow solid. The crude product was suspended in 3:1 diethyl ether−hexanes (10 mL), stirred 45 min, collected by vacuum filtration, and dried to afford racemic iodolactam *rac*-**11** (503 mg, 1.0 mmol, 55%) as a cream-colored solid: mp 180−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.20−5.03 (m, 3H), 4.62 (br m, 1H), 4.43 (br t, J = 4.3 Hz, 1H), 4.18 (m, 1H), 2.73 (br m, 1H), 2.62 (d, J = 12.5 Hz, 1H), 2.51 (dd, J = 16.0, 5.5 Hz, 1H), 2.34−2.25 (m, 1H), 2.14−2.02 (m, 1H), 1.53 (s, 9H); ESI MS *m*/*z* 401 $[C_{20}H_{25}IN_2O_5 - C_5H_8O_2 + H]^+$.

Acknowledgment. We thank Dr. Joel C. Barrish for a critical review of the manuscript.

Supporting Information Available: Experimental procedures for the preparation of compounds **6**−**10** and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.