Tetrahedron Letters 49 (2008) 5141–5143

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

RCM-mediated stereoselective synthesis of three novel tetrahydroisoquinoline tetracyclic core frameworks

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ARTICLE INFO

Article history:
Received 27 May 2008
Revised 19 June 2008
Accepted 20 June 2008
Available online 25 June 2008

Keywords:
Tetrahydroisoquinoline
Ring-closing metathesis

ABSTRACT

Three novel tetrahydroisoquinoline tetracyclic core frameworks were stereoselectively synthesized. The key steps included a ring-closing metathesis (RCM)-mediated cyclization and a subsequent intramolecular S_N2 N(O)-substituted reaction. This simple method for tetracyclic core synthesis facilitates the further exploration of the chemical space of tetrahydroisoquinoline alkaloids.

The antitumor antibiotics belonging to the tetrahydroisoquinoline family have been studied thoroughly over the past 33 years, since the isolation of naphthyridinomycin (Fig. 1) in 1974.[1] These tetrahydroisoquinoline alkaloids contain multichiral stereogenic centers, and display a range of antitumor activities and antimicrobial activity. Therefore, it is meaningful to design and optimize simple tetrahydroisoquinoline alkaloid analogues as new lead compounds. To date, several total synthesis of tetrahydroisoquinoline alkaloids were reported.[2] Here, we report a potentially general and concise method of constructing three densely functionalized tetracyclic tetrahydroisoquinoline core frameworks (Fig. 2): general core **1**, **2** (with an 'anti-N-ring bridge'), and a unique ether-containing tetracyclic core **3**, via the ring-closing metathesis (RCM) reaction of α-amino acylamide, that we reported previously,[3] and the intramolecular S_N2 reaction. This simple method could be applied to the total synthesis of related natural products and further exploration of their chemical space.

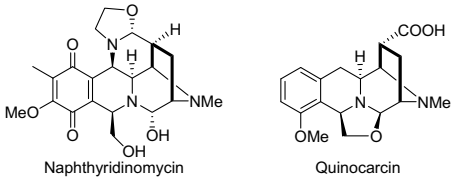

Figure 1. Natural tetrahydroisoquinoline alkaloids.

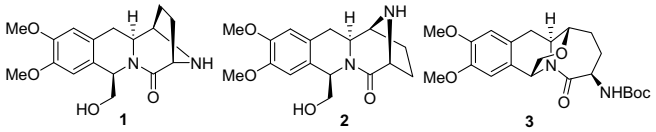

Figure 2. Tetrahydroisoquinoline tetracyclic core frameworks **1**–**3**.

Two core structures of this family are the quinone **a** and the aromatic core **b** (Fig. 3). The quinone core **a** can be easily constructed by the oxidation of aromatic core **b**. The goal of this study was to construct highly strained tetrahydroisoquinoline core frameworks containing several reactive groups, which could be useful key intermediates for the further chemical modification.

The synthesis of the intermediate aldehyde **7** is outlined in Scheme 1. We started from tetrahydroisoquinoline-3-carboxylic acid ester **4**, which was prepared from L-dopa methyl ester by the Pictet–Splender reaction, as reported previously.[4] Protection of the nitrogen of **4** by the Boc group produced **5**, which was transformed into the methylated product **6** by treatment with CH_3I/K_2CO_3 in acetone at room temperature. The reduction of **6** with $LiAlH_4$ and its subsequent oxidation under Swern conditions produced the single product **7**.

Treatment of **7** with allylic bromide with Zn mediation in aqueous NH_4Cl medium generated the alcohol **8** with an *R* configuration in quantitative yield (diastereomeric ratio >20:1 by ^1H NMR) (Scheme 2).[5] However, the addition reaction of **7** with allylmagnesium bromide produced alcohol **8** with low diastereoselectivity (69% yield, *S*/*R* = 1/3 by ^1H NMR). With **8** in hand, the amine intermediate **9** was readily produced by deprotection with TFA in

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doi:10.1016/j.tetlet.2008.06.094

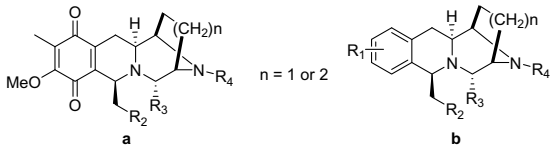
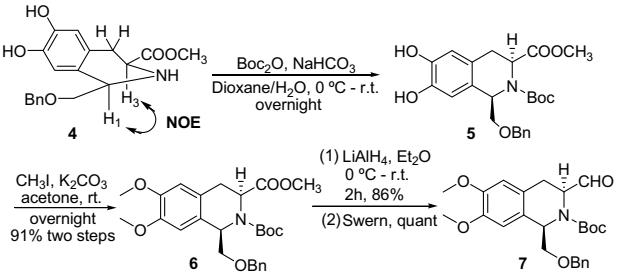
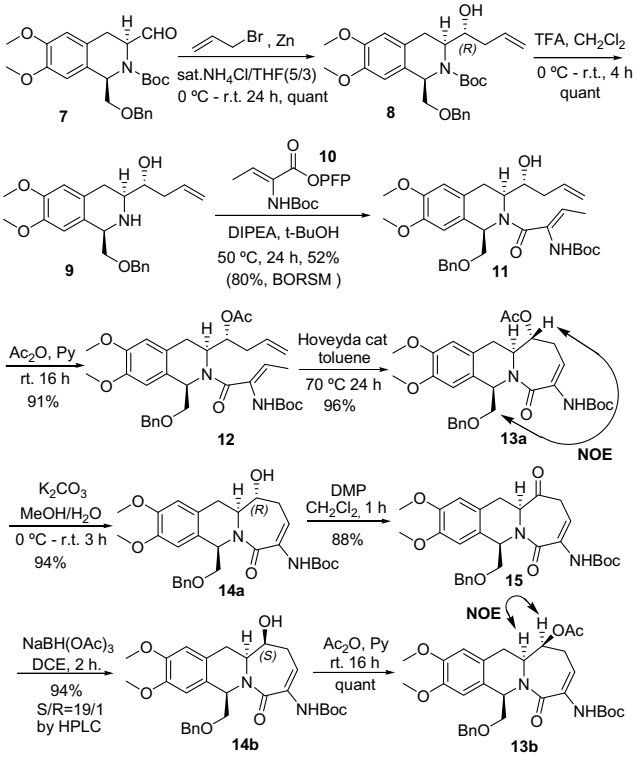


Figure 3. General structures of the tetrahydroisoquinolines.

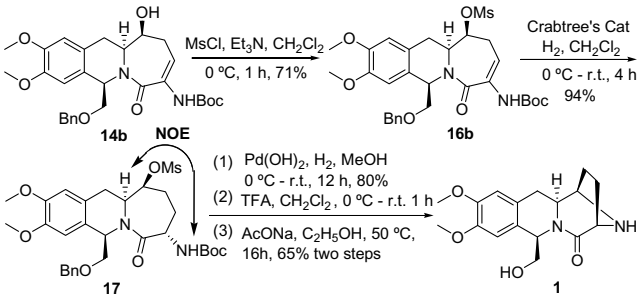


Scheme 1. Synthesis of the segment **7**.

CH_2Cl_2. The synthesis of the amide intermediate **11** was problematic because of the very low reactivity of the NH at the 2-position. When the hydroxyl at the 11-position was protected, the condensation reaction did not proceed at all, regardless of the conventional coupling reagent used. However, the reaction of free hydroxyl intermediate **9** with the active pentafluorophenyl (PFP) ester **10**[3b] and *N*,*N*-diisopropylethylamine (DIPEA) as the base in *t*-BuOH at 50 °C had taken place smoothly, the product **11** was produced in an 80% yield based on 65% conversion. After the protection of the hydroxyl with an acetyl group, the key tricycle **13a** was produced by RCM of the α-amino acrylamine, in a high yield.



Scheme 2. Synthesis of the key intermediates **14a** and **14b**.



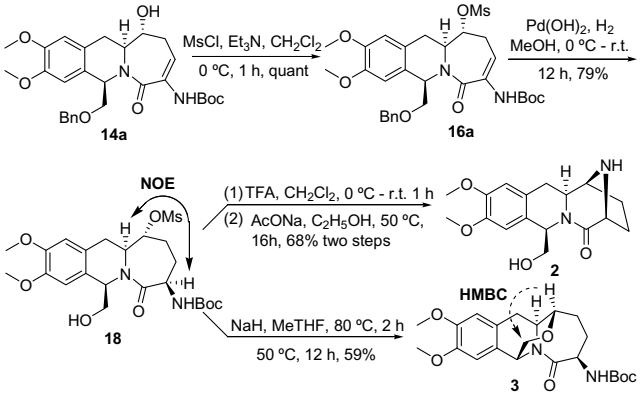
Scheme 3. Synthesis of the tetracyclic core framework **1**.

The recyclable Hoveyda catalyst was better than the Grubbs II catalyst. After the deprotection of the acetyl group, the product **14a** was conveniently transformed to its isomer **14b**, when treated with Dess–Martin periodinane (DMP), followed by its reduction with $NaBH(OAc)_3$ (83% in two steps, *S*/*R* = 19/1 by HPLC). The configurations were confirmed by nuclear Overhauser effect (NOE) analysis of their acetylates. The two epimers **14a** and **14b** were easily separated by silica-gel column chromatography and were used in the subsequent synthesis of compounds **1** and **2**, respectively.

The alcohol **14b** was transformed to methanesulfonate **16b** with a minor alkene byproduct formed simultaneously under these reaction conditions, as a result of the elimination of the MsO group (Scheme 3). Compound **16b** was hydrogenated in the presence of Crabtree's catalyst,[6] with hydrogen bubbled through a solution of CH_2Cl_2, forming the *anti* product **17** in a yield of 94%. After the deprotection of the benzyl group using $Pd(OH)_2$ and the Boc group in TFA/CH_2Cl_2, the resulting primary amine was instantly dissolved in ethanol and heated to 50 °C in the presence of AcONa,[7] forming the tetracyclic quinone **1** in a 65% yield.[8]

Mesylate **16a** was obtained under similar conditions, in quantitative yield, because there was no elimination. Subsequent hydrogenation with 20% $Pd(OH)_2$ in methanol produced a mixture of **18** and its diastereomer in a ratio of 8:1, and they were separated by silica-gel column chromatography (Scheme 4). Deprotection of the Boc group, followed by treatment with AcONa in C_2H_5OH, as shown in Scheme 3, produced the reverse N-substituted product **2** in a 68% yield.[9]

Interestingly, when compound **18** was treated with NaH in MeTHF, the intramolecular O-substituted S_N2 reaction produced the unique ether-containing tetracyclic product **3** in a 59% yield.[10] Compound **3** represents a novel framework of tetrahydroisoquinoline, which has never been reported before.



Scheme 4. Synthesis of the tetracyclic core frameworks **2** and **3**.

In summary, we have developed a simple and efficient synthesis of the tetracyclic core frameworks **1, 2** of the tetrahydroisoquinoline alkaloids containing the highly strained bicyclo[3.2.1]octane framework, and a unique ether-containing tetracyclic core **3**. This synthesis uses the powerful RCM reaction for ready access to the α-amino α,β-unsaturated caprolactam **13a**, and the intramolecular S_N2 reaction of the lactams **17** and **18** to produce the highly strained tetracycles. Further structural modifications to compounds **1**, **2**, and **3** to explore their chemical space are in progress in our laboratory.

Acknowledgments

This work was supported financially by the National Natural Science Foundation of China (Grants 30572242, 30725049) and 863 Hi-Tech Program Grant 2006AA09Z442.

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8. *Characterization data of compound* **1**: $[\alpha]_D^{22}$ −65 (*c* 0.1450, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.70 (s, 1H), 6.63 (s, 1H), 5.19 (dd, *J* = 3.6, 6.3 Hz, 1H), 3.80–3.90 (m, 7H), 3.71–3.76 (m, 1H), 3.58–3.67 (m, 3H), 2.79 (t, *J* = 13.5 Hz, 1H), 2.51 (dd, *J* = 1.8, 14.7 Hz, 1H), 2.14–2.21 (m, 1H), 2.01–2.11 (m, 2H), 1.90–1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 148.4, 148.3, 127.8, 125.5, 111.0, 110.8, 70.1, 62.3, 61.0, 58.2, 57.7, 56.3, 56.2, 33.1, 32.0, 22.6. HRMS (EI) calcd for $C_{17}H_{22}N_2O_4$ (M^+) 318.1580, found 318.1579, error: −0.3 ppm.
9. *Characterization data of compound* **2**: $[\alpha]_D^{22}$ −145 (*c* 0.3900, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.69 (s, 1H), 6.62 (s, 1H), 4.94 (t, *J* = 3.3 Hz, 1H), 4.00 (dd, *J* = 3.0, 11.7 Hz, 1H), 3.80–3.90 (m, 7H), 3.65 (dd, *J* = 4.5, 12.0 Hz, 1H), 3.59 (t, *J* = 2.7 Hz, 1H), 2.95–3.10 (m, 2H), 2.55 (d, *J* = 13.2 Hz, 1H), 1.90–2.05 (m, 3H), 1.58–1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.3, 148.3, 148.0, 129.1, 126.4, 111.1, 110.4, 68.8, 61.5, 61.1, 60.3, 57.7, 56.3, 56.1, 36.7, 31.7, 28.9. HRMS (EI) calcd for $C_{17}H_{22}N_2O_4$ (M^+) 318.1580, found 318.1590, error: 3.1 ppm.
10. *Characterization data of compound* **3**: $[\alpha]_D^{22}$ −46 (*c* 0.4200, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.67 (s, 1H), 6.61 (s, 1H), 5.91 (d, *J* = 6.6 Hz, 1H), 5.32 (s, 1H), 4.90–4.98 (m, 1H), 4.24 (d, *J* = 8.1 Hz, 1H), 4.17 (dd, *J* = 3.3, 11.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.32–3.43 (m, 2H), 2.93 (d, *J* = 17.7 Hz, 1H), 2.02–2.27 (m, 3H), 1.75–1.87 (m, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 175.1, 155.2, 148.7, 147.8, 125.4, 125.3, 110.5, 109.0, 79.7, 74.3, 66.7, 56.0, 55.9, 53.2, 51.3, 50.2, 32.3, 31.2, 31.0, 29.7, 28.4. HRMS (EI) calcd for $C_{22}H_{30}N_2O_6$ (M^+) 418.2104, found 418.2101, error: −0.7 ppm.