An Approach to the Synthesis of Enantiopure Tetrahydroisoquinoline via a Key Asymmetric Ugi Reaction

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Abstract: An approach to the synthesis of the multisubstituted tetrahydroisoquinoline featuring an asymmetric Ugi reaction of α-amino acid, aromatic aldehyde and an isocyanide has been developed. The promising utility of the strategy is demonstrated by a synthesis of an enantiopure functionalized 1,3-*trans*-tetrahydroisoquinolin-4-ol from natural L-valine. The configuration of the two stereocenters at C-1 and C-4, generated in the Ugi reaction and Pomeranz–Fritsch-type cyclization separately, was controlled very well and determined by NMR studies.

Key words: Ugi reaction, α-amino acid, aromatic aldehyde, tetrahydroisoquinoline, asymmetric synthesis

Tetrahydroisoquinolines are the privileged structural units found in a number of bioactive and medical molecules including natural products (Figure 1). Many substituted tetrahydroisoquinoline compounds possess a wide range of important properties in pharmacy such as antitumor and antibiotic,[1] antineoplastic,[2] anti-inflammatory and antiallergic,[3] antiviral,[4] central nerve system (CNS) depressant activities[5] and so on. Furthermore, some of them have been used as potent antimalarial,[6] ionotropic glutamate receptor antagonist,[7] and therapeutic agents for imagining VMAT-2 in brain.[8] Therefore, the development of methods for the asymmetric construction of multisubstituted tetrahydroisoquinolines has attracted much attention.[9] For the stereoselective synthesis of polysubstituted tetrahydroisoquinolines, the effective control of the configuration of those stereocenters on the ring, especially C-1 position, is a key issue.

Up to now, stereocontrol at C-1 on tetrahydroisoquinoline ring has been achieved from appropriate chiral substrates mostly by stereoselective Pictet–Spengler reaction,[9d,g,k,n] radical cyclization of imine[9e] or reduction of dihydroisoquinoline.[9a,l,n] Recently, we became interested in the development of asymmetric Ugi reaction based on chiral substrates and their application in synthesis.[10] As part of the research, we report here a new route to the synthesis of enantiopure 4-hydroxy-1,3-*trans*-tetrahydroisoquinolines featuring an asymmetric Ugi reaction with chiral α-amino acid, by which the chiral center at C-1 is formed in high stereoselectivity (Scheme 1). Ugi five-center four-component reactions (U-5C-4CR) of an α-amino acid, an aldehyde and an isocyanide in a nucleophilic solvent (e.g. methanol) have been reported to produce a 1,1′-iminodicarboxylic acid derivative with a new chiral center.[11] Although 1,1′-iminodicarboxylic acid derivatives have showed some biological[12] and synthetic[12a,c,13] importance, the application of the compound as a key intermediate in the construction of tetrahydroisoquinolines is seldom reported. Only Cuifolini group employed a related asymmetric Ugi reaction to prepare a cyclization precursor for the synthesis of quinocarcin framework very recently; however, the subsequent formation of tetrahydroisoquinoline ring has not been described.[14]

Thus, our tetrahydroisoquinoline synthesis began with the Ugi reaction of L-(*S*)-valine (**5**), vanillin methyl ether (**6**) and isocyanoalkyl alkyl carbonate **7**. Compound **7** is a po-

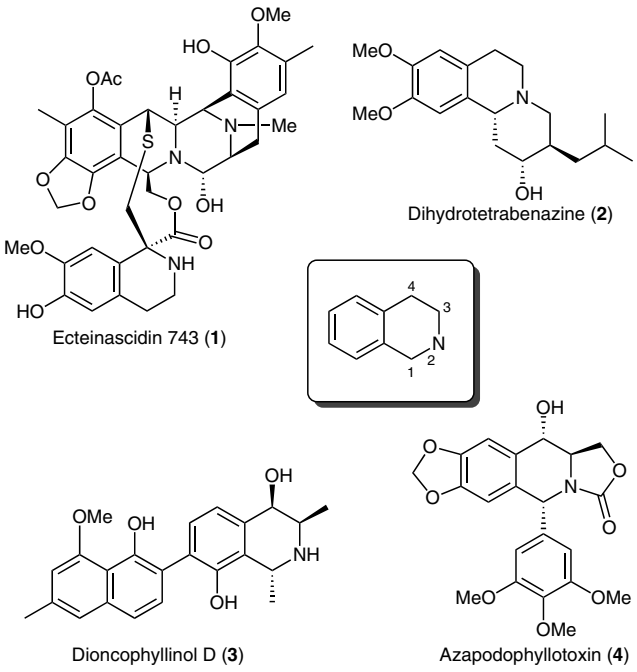
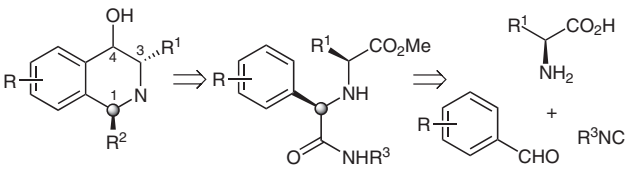


Figure 1 Several bioactive tetrahydroisoquinoline alkaloids



Scheme 1 Our synthetic strategy for tetrahydroisoquinoline

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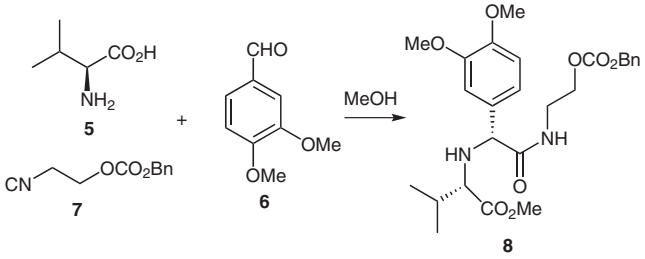
tential convertible isonitrile to permit post-modification of the C-terminal amide formed in the reaction,[15] so that the substituents at C-1 in the resultant tetrahydroisoquinolines are probably not limited only to amides. In previous studies on the U-5C-4CR, the case utilizing electron-rich aromatic aldehydes is limited due to their reduced electrophilicity.[16] Indeed, condensation of **5**, **6** and **7** in methanol at room temperature proceeded relatively slow, and gave the desired products **8** in 59% yield after stirring for three days concomitant with 26% recovered aldehyde **6** (Table 1, entry 1). Longer reaction time did not seem to facilitate further conversion of the materials. Elevating the temperature accelerated the rate of the reaction, but decreased the yield of product **8** and of recovered aldehyde **6** (entry 2). Although $TiCl_4$ was reported as an efficient catalyst in this U-5C-4CR with some aromatic aldehydes,[16] for our reaction, addition of some Lewis acids including $TiCl_4$ led to a drop in yield (entries 3–5). Only molecular sieves showed a beneficial effect on the reaction, affording **8**[17] and **6** in slightly improved yield (entry 6). Gratifyingly, excellent diastereoselectivity was observed in the reaction, and only single product isomer was obtained. The absolute configuration of the new chiral center in **8** was unknown at this stage, and could be determined readily after further construction of the tetrahydroisoquinoline ring.

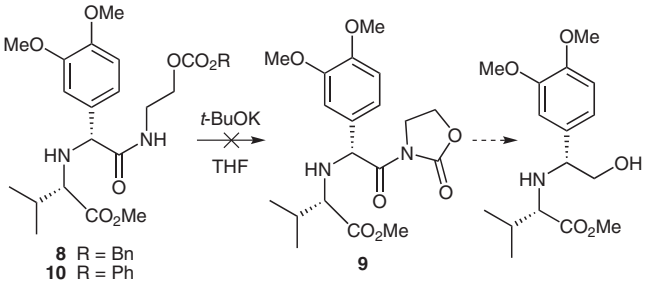
Table 1 Investigation of Asymmetric Ugi Reaction of **5**, **6** and **7** in Methanol[a]



Entry	Time (h)	Additive	T (°C)	Yield of **8**	Recovered **6**
1	72	–	r.t.	59%	26%
2	12	–	50	52%	11%
3	48	$TiCl_4$ (5 mol%)	r.t.	38%	24%
4	48	$ZnCl_2$ (100 mol%)	r.t.	50%	42%
5	48	$Sc(OTf)_3$ (10 mol%)	r.t.	36%	22%
6	72	4 Å MS	r.t.	64%	31%
7	12	4 Å MS	50	59%	14%

[a] Reaction conditions: **5**, **6** and **7** were used in a ratio of 1:1:1, and the concentration was 0.3 mol/L.

To obtain more tetrahydroisoquinolines with different substituent at C-1, the selective conversion of the amide bond generated in the Ugi reactions is desirable and necessary. Therefore, our efforts focused on the transformation of Ugi product **8** to the corresponding *N*-acyloxazolidione **9**, in which the amide bond was easily cleaved by addition of a nucleophile or reduction according to literature methods (Scheme 2).[15] However, under various conditions only complex mixtures containing none of the desired *N*-acyloxazolidione **9** were obtained.

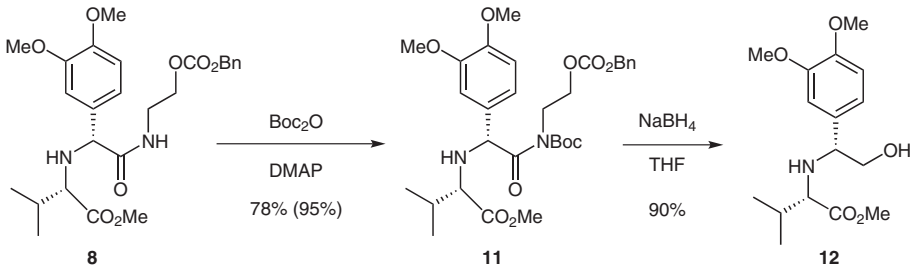


Scheme 2 Attempt on the formation of oxazolidinone

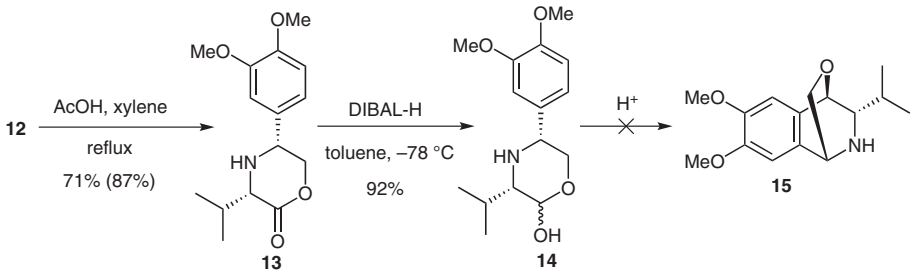
Similar results were observed when **10** was employed instead of **8** to produce **9**. Fortunately, the amide bond in **8** could be activated via protection of the amide nitrogen as the *tert*-butyl carbamate. Thus, **8** was treated with Boc_2O in the presence of DMAP to give the desired product **11** in 78% yield, along with a small amount of the recovered material **8** (18%), which could be transformed to **11** once again in the same yield. Under these conditions the free secondary amino group did not react with Boc_2O at all. Acyl carbamate **11** was easily reduced to alcohol **12** as a single isomer with $NaBH_4$ in a THF–H_2O mixture, whereas the methyl ester group remained intact (Scheme 3). The introduction of the hydroxyl function could enrich variation of structure at the position by different post-transformation. The subsequent reduction of ester **12** to the corresponding aldehyde using DIBAL-H was unsuccessful probably owing to the presence of the free hydroxyl and amino groups, and afforded a complex mixture which could not form the tetrahydroisoquinoline ring by Pomeranz–Fritsch-type reaction[18] under acidic conditions.

Thus we tried to construct tetrahydroisoquinoline via lactone **13** where interference of hydroxyl group could be avoided in the subsequent reduction (Scheme 4). After much experimentation, refluxing of **12** in xylene in the presence of acetic acid gave the desired morpholin-2-one **13** in 71% yield (87% based on conversion). Treatment of **13** with DIBAL-H smoothly furnished the corresponding hemiacetal **14** as a mixture of two diastereoisomers, a potential precursor for Pomeranz–Fritsch cyclization. However, all attempts to cyclize failed to provide the desired tetrahydroisoquinoline **15** probably owing to disfavored configuration.

Therefore, the synthetic route was adjusted as shown in Scheme 5. Protection of alcohol **12** as TBS ether gave **16**. Reduction of methyl ester in **16** with $LiAlH_4$ furnished alcohol **17**. By virtue of the new hydroxyl group, the secondary amine **17** was masked as aminonitrile **18** by a two-step sequence involving formation and opening of oxazolidine ring. Oxidation of the primary alcohol to the cor-

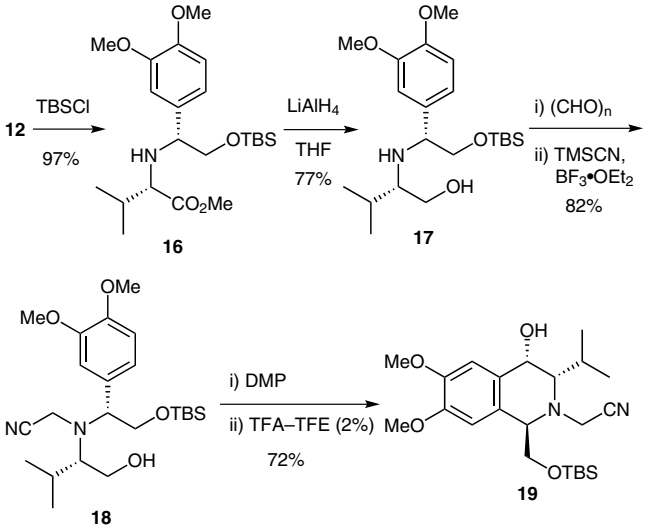


Scheme 3 Conversion of **8** into amino alcohol **12**; the yield in parentheses is based on conversion



Scheme 4 Attempt on construction of tetrahydroisoquinoline **15** via **13**

responding aldehyde with Dess–Martin periodinane resulted in the cyclization precursor, which was stirred in TFE containing 2% TFA at –10 °C to give the desired tetrahydroisoquinolin-4-ol **19**[19] in 72% yield over two steps, along with recovered aldehyde (20%). The key cyclization proceeded with excellent diastereoselectivity, and the single isomer **19** was obtained exclusively.



Scheme 5 Stereoselective synthesis of tetrahydroisoquinolin-4-ol **19** from **12**; DMP = Dess–Martin periodinane, TFA = trifluoroacetic acid, TFE = trifluoroethanol

The configuration of the cyclic compound **19** was analyzed by detailed NMR studies. In its NOESY HNMR spectra, H-3 (δ = 2.73 ppm) has obvious correlation with H-4 (δ = 4.57 ppm), that show *cis* configuration relationship between the substituent at C-3 and C-4 (Figure 2). Whereas the observation of correlation not between H-3 and H-1 (δ = 3.99 ppm) but between H-3 and H-a (δ = 3.74 and 3.86 ppm) reveals 1,3-*trans*-configuration (Figure 2). Consequently, the absolute configuration of C-1 and C-4 in **19** was determined to *R* and *S*, respectively. Hence Ugi product **8** from (*S*)-valine should have the *S*,*R* configuration. This result supported the stereochemistry of the similar Ugi reactions employing primary α-amino acids in the most reports earlier.[11c–f] Namely, the newly formed stereogenic center of the major isomer has the reverse configuration to the amino acids employed. Ciufolini group reported the converse stereoinduction in favor of (*S*,*S*)-product on the Ugi reaction with various (*S*)-amino acids including valine and aromatic aldehydes, but this general stereochemical conclusion was deduced just by a particular example, the cyclic amide derived from an Ugi product using (*S*)-glutamic acid 5-methyl ester.[15] Nevertheless, the new route opens an efficient access to enantiopure 1,3-*trans*-tetrahydroisoquinolin-4-ols using α-amino acids as starting material. On the other hand, 1,3-*cis*-tetrahydroisoquinolin-4-ols such as **20** could also be possibly prepared by this approach from optically active serine, in which the inherent hydroxyl group could be converted into aldehyde to serve for Pomeranz–Fritsch-type cyclization at appropriate stage (Scheme 6). Some important alkaloids including ecteinascidins and naphthridinomycins contain the 4-oxidized 1,3-*cis*-tetrahydroisoquinoline structure similar to **20**.

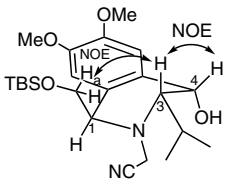
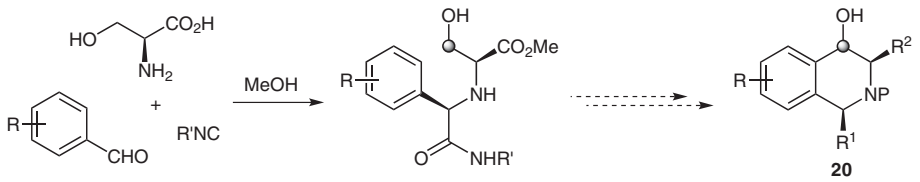


Figure 2 Determination of the configuration of **19**



Scheme 6 Devised strategy to 1,3-*cis*-tetrahydroisoquinoline from L-serine

In summary, a new approach to the construction of the chiral 1,3-substituted tetrahydroisoquinolin-4-ol was developed. 1,1′-Iminodicarboxylic acid derivative such as **8**, swiftly assembled via asymmetric Ugi reaction of α-amino acid, aromatic aldehyde and isocyanide in alcohol, was employed as a key intermediate to synthesize tetrahydroisoquinoline compound for the first time. By this approach, (*1R*,*3S*,*4S*)-tetrahydroisoquinolin-4-ol **19** was synthesized conveniently from L-valine in nine steps with high stereoselectivity. On the basis of excellent stereoinduction of the chiral substrates in the Ugi condensation and Pomeranz–Fritsch-type cyclization, stereochemistry of the two new chiral centers was controlled well. Further efforts to utilize this approach for asymmetric synthesis of more tetrahydroisoquinoline members from various α-amino acids and aromatic aldehydes are currently under way in our lab.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References and Notes

(1) (a) Kim, K. H.; Lee, I. K.; Piao, C. J.; Choi, S. U.; Lee, J. H.; Kim, Y. S.; Lee, K. R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4487. (b) Liu, Y.-Q.; Yang, L.; Tian, X. *Curr. Bioact. Compd.* **2007**, *3*, 37. (c) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545. (d) Scott, J.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (e) Ida, A.; Kano, M.; Kubota, Y.; Koga, K.; Tomioka, K. *Chem. Pharm. Bull.* **2000**, *48*, 486.

(2) (a) Stingl, J.; Andersen, R. J.; Emerman, J. T. *Cancer Chemother. Pharmacol.* **1992**, *30*, 401. (b) Pathirana, C.; Andersen, R. J. *J. Am. Chem. Soc.* **1986**, *108*, 8288.

(3) (a) Alberte, R. S.; Roschek, J. R.; William, P.; Dan, L. US Patent US20100009927, **2010**. (b) Ranieri, R. L.; McLaughlin, J. L. *J. Org. Chem.* **1976**, *41*, 319.

(4) (a) Bringmann, G.; Gunther, C.; Saeb, W.; Mies, J.; Brun, R.; Ake Assi, L. *Phytochemistry* **2000**, *54*, 337. (b) Bentley, K. W. *Nat. Prod. Rep.* **2002**, *19*, 332.

(5) Onoda, T.; Takikawa, Y.; Fujimoto, T.; Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2009**, 1041.

(6) Buchanan, M. S.; Davis, R. A.; Duffy, S.; Avery, V. M.; Quinn, R. J. *J. Nat. Prod.* **2009**, *72*, 1541.

(7) Chimirri, A.; De Luca, L.; Ferro, S.; De Sarro, G.; Ciranna, L.; Gitto, R. *ChemMedChem* **2009**, *4*, 917.

(8) (a) Yu, Q.-S.; Luo, W.; Deschamps, J.; Holloway, H. W.; Kopajtic, T.; Katz, J. L.; Brossi, A.; Greig, N. H. *ACS Med. Chem. Lett.* **2010**, *1*, 105. (b) Hayden, M. R.; Leavitt, B. R.; Yasothan, U.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2009**, *8*, 17. (c) Kilbourn, M. R.; Hockley, B.; Lee, L.; Hou, C.; Goswami, R.; Ponde, D. E.; Kung, M.-P.; Kung, H. F. *Nucl. Med. Biol.* **2007**, *34*, 233. (d) Goswami, R.; Ponde, D. E.; Kung, M.-P.; Hou, C.; Kilbourn, M. R.; Kung, H. F. *Nucl. Med. Biol.* **2006**, *33*, 685. (e) Lee, C. L.; Van der Borght, T.; Sherman, P. S.; Frey, K. A.; Kilbourn, M. R. *J. Med. Chem.* **1996**, *39*, 191.

(9) (a) Lee, K. M.; Kima, J. C.; Kang, P.; Lee, W. K.; Eumb, H.; Ha, H.-J. *Tetrahedron* **2012**, *68*, 883. (b) Srivastava, A. K.; Koh, M.; Park, S. B. *Chem. Eur. J.* **2011**, *17*, 4905. (c) Aubry, S.; Pellet-Rostaing, S.; Lemaire, M. *Eur. J. Org. Chem.* **2007**, 5212. (d) Chen, X.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 3962. (e) Fishlock, D.; Williams, R. M. *Org. Lett.* **2006**, *8*, 3299. (f) Chen, X.; Chen, J.; Zhu, J. *Synthesis* **2006**, 4081. (g) Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684. (h) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397. (i) Marcantoni, E.; Petrini, M.; Profeta, R. *Tetrahedron Lett.* **2004**, *45*, 2133. (j) Saitoh, T.; Shikiya, K.; Horiguchi, Y.; Sano, T. *Chem. Pharm. Bull.* **2003**, *51*, 667. (k) De Paolis, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2003**, 2896. (l) Ohba, M.; Nishimura, Y.; Kato, M.; Fujll, T. *Tetrahedron* **1999**, *55*, 4999. (m) Tellitu, I.; Badfa, D.; Domfnguez, E.; Garcfa, F. J. *Tetrahedron: Asymmetry* **2002**, *13*, 1929. (n) Brossi, A.; Focella, A.; Teitel, S. *Helv. Chim. Acta* **1972**, *55*, 15.

(10) (a) Li, S.; Chen, R.; Liu, X.; Pan, L.; Xia, L.; Chen, X. *Synlett* **2012**, *23*, 1985. (b) Zhu, D.; Xia, L.; Pan, L.; Li, S.; Chen, R.; Mou, Y.; Chen, X. *J. Org. Chem.* **2012**, *77*, 1386. (c) Zhu, D.; Chen, R.; Liang, H.; Li, S.; Pan, L.; Chen, X. *Synlett* **2010**, 897.

(11) (a) Demharter, A.; Horl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 173. (b) Ugi, I.; Demharter, A.; Hiirl, W.; Sehmid, T. *Tetrahedron* **1996**, *52*, 11657. (c) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661. (d) Sollis, S. L. *J. Org. Chem.* **2005**, *70*, 4735. (e) Sung, K.; Chen, F.-L.; Chung, M.-J. *Mol. Divers.* **2003**, *6*, 213. (f) Dyker, G.; Breitenstein, K.; Henkel, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1929.

(12) (a) Hayashi, K.; Nunami, K.; Kato, J.; Yoneda, N.; Kubo, M.; Ochiai, T.; Ishida, R. *J. Med. Chem.* **1989**, *32*, 289. (b) Blankley, C. J.; Kaltenbronn, J. S.; DeJohn, D. E.; Werner, A.; Bennett, L. R.; Bobowski, G.; Krolls, U.; Johnson, D. R.; Pearlman, W. M.; Hoefle, M. L.; Essenburg, A. D.; Cohen, D. M.; Kaplan, H. R. *J. Med. Chem.* **1987**, *30*, 992. (c) Maycock, A. L.; DeSousa, D. M.; Payne, L. G.; Broeke, J. T.; Wu, M. T.; Patchett, A. A. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 963. (d) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; Broeke, J. T.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.;

Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature (London)* **1980**, *288*, 280.
(13) Sollis, S. L. *J. Org. Chem.* **2005**, *70*, 4735.
(14) Turner, C. D.; Ciufolini, M. A. *Org. Lett.* **2012**, *14*, 4970.
(15) (a) Rikimaru, K.; Yanagisawa, A.; Kan, T.; Fukuyama, T. *Synlett* **2004**, 41. (b) Kennedy, A. L.; Fryer, A. M.; Josey, J. A. *Org. Lett.* **2002**, *4*, 1167. (c) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411.
(16) Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M. A. *Org. Lett.* **2004**, *6*, 3281.
(17) **8**: $[\alpha]_D^{20}$ –74 (*c* = 0.6, in CH_2Cl_2). IR (neat): 3372, 2960, 2838, 1739, 1678, 1514, 1461, 1395, 1262, 1147, 1026, 903, 789, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.37 (m, 5 H), 6.78–6.91 (m, 3 H), 5.13 (s, 2 H), 4.15–4.28 (m, 2 H), 4.13 (s, 1 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.69 (s, 3 H), 3.43–3.65 (m, 2 H), 2.85 (d, *J* = 6.0 Hz, 1 H), 1.91–2.01 (m, 1 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 172.2, 154.9, 149.3, 149.1, 143.0, 130.3, 128.6, 128.3, 120.9, 111.1, 110.3, 69.8, 66.6, 66.1, 65.2, 64.0, 55.8, 55.7, 51.6, 38.6, 31.3, 19.4, 18.4. HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_8$: 503.2393; found: 503.2391.
(18) (a) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43. (b) Scott, J. D.; Williams, R. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1463. (c) Głuszyńska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2359.
(19) **19**: $[\alpha]_D^{20}$ +3 (*c* = 0.7, in CH_2Cl_2). IR (neat): 3498, 2954, 2928, 2859, 2710, 2610, 2252, 1608, 1510, 1462, 1343, 1311, 1251, 1221, 1152, 1108, 1046, 934, 838, 775, 666, 637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.80 (s, 1 H), 6.77 (s, 1 H), 4.57 (br t, *J* = 6.2 Hz, 1 H), 3.99 (t, *J* = 5.8 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.86–3.88 (m, 2 H), 3.74 (dd, *J* = 5.8, 9.9 Hz, 1 H), 3.59 (d, *J* = 17.5 Hz, 1 H), 2.73 (dd, *J* = 2.4, 10.5 Hz, 1 H), 2.08–2.12 (m, 1 H), 1.59 (d, *J* = 2.9 Hz, 1 H), 1.10 (d, *J* = 4.5 Hz, 3 H), 1.09 (d, *J* = 4.6 Hz, 3 H), 0.85 (s, 9 H), 0.01 (s, 3 H), –0.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 148.6, 129.1, 125.9, 118.8, 111.6, 111.1, 66.8, 64.8, 63.7, 62.2, 55.9, 38.7, 25.8, 20.3, 20.0, 18.1, –5.4, –5.6. HRMS (ESI$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{39}N_2O_4Si$: 435.2679; found: 435.2675.