ORGANIC LETTERS

2011
Vol. 13, No. 4
796–799

Stereoselective Synthesis of 2,6-*cis*- and 2,6-*trans*-Piperidines through Organocatalytic Aza-Michael Reactions: A Facile Synthesis of (+)-Myrtine and (−)-Epimyrtine

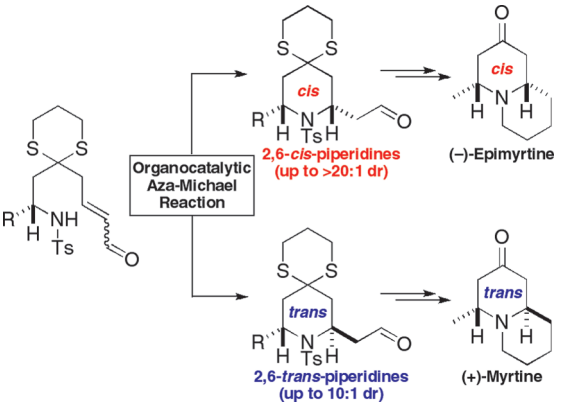
Yongcheng Ying, Hyoungsu Kim, and Jiyong Hong*

Department of Chemistry, Duke University, Durham, North Carolina 27708, United States

jiyong.hong@duke.edu

Received December 17, 2010

ABSTRACT



Both 2,6-*cis*- and 2,6-*trans*-piperidines were prepared from common substrates through organocatalytic aza-Michael reactions promoted by the *gem*-disubstituent effect in conjunction with dithiane coupling reactions. The organocatalytic aza-Michael reaction enabled a facile synthesis of (+)-myrtine and (−)-epimyrtine from a common substrate.

Structurally complex piperidines are found in a wide range of biologically interesting natural products. In particular, 2,6-disubstituted piperidines have attracted considerable interest because of their therapeutic potential.[1] Although an increasing amount of interest has focused on the generation of 2,6-disubstituted piperidines,[2,3] there are few methods that enable the synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from a common substrate. Moreover, it is surprising that the organocatalytic aza-Michael reaction has rarely been used for the stereoselective synthesis of piperidines.[4,5]

(1) (a) Struntz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 89−193. (b) Schneider, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155−299.

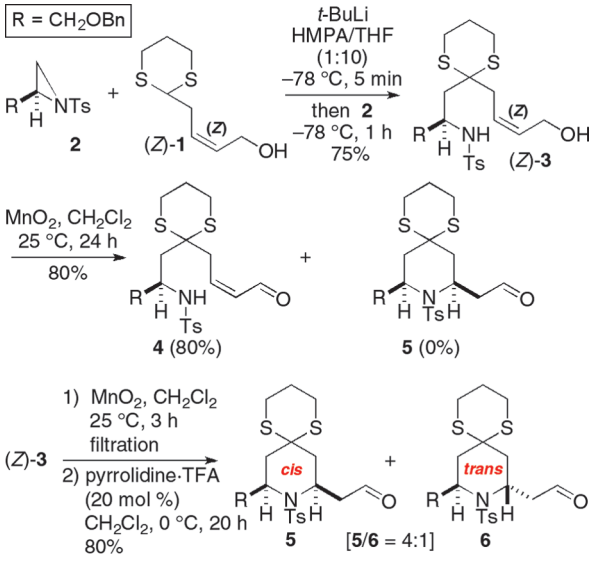
(2) For reviews on the synthesis of 2,6-disubstituted piperidines, see: (a) Weintraub, J. S.; Sabol, P. M.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (c) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80.

(3) For recent examples of the synthesis of 2,6-disubstituted piperidines, see: (a) Gnamm, C.; Krauter, C. M.; Broedner, K.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 2050–2054. (b) Gnamm, C.; Broedner, K.; Krauter, C. M.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 10514–10532. (c) Kumar, R. S. C.; Sreedhar, E.; Reddy, V. G.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymmetry* **2009**, *20*, 1160–1163. (d) Kumar, R. S. C.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Chem. Lett.* **2009**, *38*, 564–565. (e) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808–1811.

10.1021/ol103064f
Published on Web 01/20/2011

Herein, we report the stereoselective synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from common substrates through the organocatalytic aza-Michael reaction promoted by the *gem*-disubstituent effect and its application to a facile synthesis of (+)-myrtine and (−)-epimyrtine.

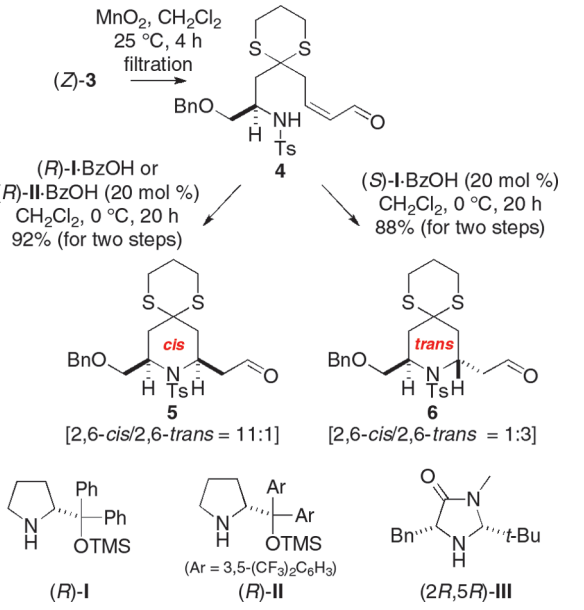
Scheme 1. Synthesis of 2,6-*cis*-Piperidine **5** through an Intramolecular Aza-Michael Reaction



To test the feasibility of the tandem allylic oxidation/aza-Michael reaction[6] in the synthesis of 2,6-disubstituted piperidines, we prepared substrate (*Z*)-**3** by coupling[7] allyl alcohol (*Z*)-**1**[6] with the readily available Ts-protected chiral aziridine **2** and subjected it to MnO_2-oxidation conditions (Scheme 1). However, due to the poor nucleophilicity of sulfonamide **4**, the tandem allylic oxidation/aza-Michael reaction of (*Z*)-**3** in the presence of MnO_2 failed to provide the desired 2,6-*cis*-piperidine **5**. Instead, it resulted in the exclusive formation of the intermediate (*Z*)-enal **4** (80%).

We hypothesized that the activation of the conjugate acceptor would help overcome the poor nucleophilicity of **4** in the aza-Michael reaction. To test this hypothesis, we converted **4** to the corresponding iminium ion by treatment with pyrrolidine·TFA (Scheme 1). As expected, the iminium activation of **4** dramatically promoted the aza-Michael reaction to successfully provide the desired 2,6-*cis*-piperidine **5**.[8] However, the stereoselectivity of the *substrate-controlled* aza-Michael reaction was modest (**5**:**6** = 4:1).

Scheme 2. Organocatalytic Aza-Michael Reactions for the Synthesis of 2,6-*cis*- and 2,6-*trans*-Piperidines



To further improve the stereoselectivity of the aza-Michael reaction, we decided to test chiral organocatalysts.[4,5,9] When (*R*)-**I**[10] or (*R*)-**II**[10a] was employed (Scheme 2), the desired 2,6-*cis*-piperidine **5** was obtained with good stereoselectivity (dr = 11:1).[11] The catalyst (2*R*,5*R*)-**III**[12] also provided **5**, but in modest stereoselectivity (dr = 4:1). When (*S*)-**I** was used for the aza-Michael reaction of **4**, the 2,6-*trans*-piperidine **6** was obtained as the major diastereomer (dr = 3:1), demonstrating that the synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines could be achieved from a common substrate through the organocatalytic aza-Michael reactions.[13] To the best of our

(4) For a review on the organocatalytic aza-Michael reaction, see: Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076.

(5) For examples of the synthesis of monosubstituted or benzofused piperidines by the organocatalytic aza-Michael reaction, see: (a) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51–55. (b) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. (c) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158. (d) Fustero, S.; Moscardo, J.; Jimenez, D.; Perez-Carrion, M. D.; Sanchez-Rosello, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872.

(6) For an analogous tandem allylic oxidation/oxa-Michael reaction, see: (a) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577–7581. (b) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880–2883.

(7) (a) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493–1495. (b) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247–3250. (c) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547–2557.

(8) The relative stereochemisry of the major diastereomer of the reaction was determined to be *cis* by 2D NMR spectroscopy (see the Supporting Information for details).

(9) For recent examples of organocatalytic aza-Michael reaction, see: (a) Uria, U.; Vicario, J. L.; Badia, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509–2511. (b) Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3565–3568. (c) Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636–5638. (d) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999–2002. (e) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, 4119–4124. (f) Lv, J.; Wu, H.; Wang, Y. *Eur. J. Org. Chem.* **2010**, *11*, 2073–2083.

(10) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

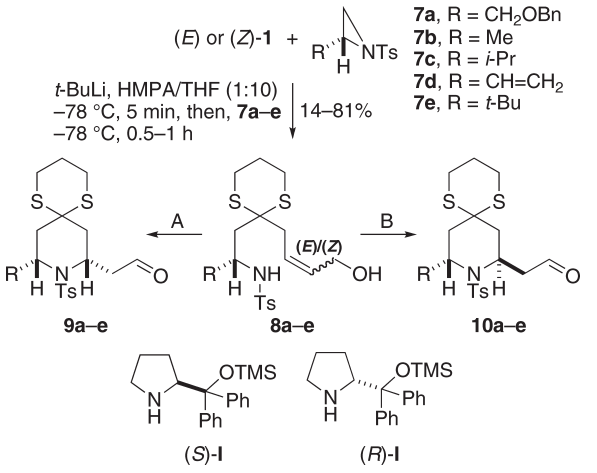
(11) A variety of solvents were tested to further optimize the reaction conditions, and CH_2Cl_2 proved to be the most effective for the reaction (see the Supporting Information for details).

(12) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.

(13) To assess the effect of protecting groups on stereochemical outcome, we prepared the corresponding Boc- and Cbz-carbamates of **4** and subjected them to the organocatalytic aza-Michael reaction conditions. Both (*R*)-**I** and (*S*)-**I** provided 2,6-*cis*-piperidines as the major diastereomer (dr = 2−20:1; see the Supporting Information for details).

knowledge, the stereoselective synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from a common substrate has not been achieved for intramolecular organocatalytic aza-Michael reaction, although it has been appeared in a few other reactions such as Ir-catalyzed allylic substitutions.[3a,b]

Table 1. Substrate Scope of the Organocatalytic Aza-Michael Reaction



entry	substrate	conditions[a]	major product (yield[b])	dr[c]
1	(*Z*)-**8a**	**A**	**9a** (91%)	11:1
		B	**10a** (82%)	1:3
	(*E*)-**8a**	**A**	**9a** (93%)	15:1
		B	**10a** (86%)	1:5
2	(*Z*)-**8b**	**A**	**9b** (90%)	>15:1
		B	**10b** (75%)	1:2
	(*E*)-**8b**	**A**	**9b** (97%)	>20:1
		B	**10b** (80%)	1:4
3	(*Z*)-**8c**	**A**	**9c** (78%)	10:1
		B	**10c** (78%)	1:8
	(*E*)-**8c**	**A**	**9c** (87%)	12:1
		B	**10c** (79%)	1:10
4	(*Z*)-**8d**	**A**	**9d** (90%)	15:1
		B	**10d** (86%)	1:1
5	(*Z*)-**8e**	**A**	NR[d]	NA[e]
		B	NR[d]	NA[e]

[a] **A**: (1) MnO_2, CH_2Cl_2, 25 °C, 3 h, filtration; (2) (*S*)-**I**·BzOH (20 mol %), CH_2Cl_2, 0 °C, 7−45 h. **B**: (1) MnO_2, CH_2Cl_2, 25 °C, 3 h, filtration; (2) (*R*)-**I**·BzOH (20 mol %), CH_2Cl_2, 0 °C, 9−67 h. [b] Combined yield of the isolated 2,6-*cis*- and 2,6-*trans*-piperidines. [c] The diastereomeric ratio (2,6-*cis*-piperidine:2,6-*trans*-piperidine) was determined by integration of the ^{1}H NMR spectrum of the crude product. [d] No reaction. [e] Not applicable.

To investigate the scope and stereochemical outcome of the organocatalytic aza-Michael reaction with respect to substituents at the C2 position, we prepared sulfonamides **8a**−**e** by coupling **1** with the commercially or readily available chiral aziridines **7a**−**e** and subjected them to the allylic oxidation/organocatalytic aza-Michael reaction (Table 1). We were pleased to find that the aza-Michael reaction of **8a**−**d** in the presence of (*S*)-**I** proceeded smoothly to provide the corresponding 2,6-*cis*-piperidines **9a**−**d** with good to excellent stereoselectivities (up to 20:1 dr, entries 1−4). In addition, when (*R*)-**I** was used for the aza-Michael reaction of **8a**−**d**, 2,6-*trans*-piperidines **10a**−**d** were obtained with modest to good stereoselectivities (up to 10:1 dr, entries 1−4). However, sterically hindered tertiary amine **8e** did not afford the desired piperidines (Table 1, entry 5). It is noteworthy that higher stereoselectivities were observed with (*E*)-enals compared with the corresponding (*Z*)-enals.

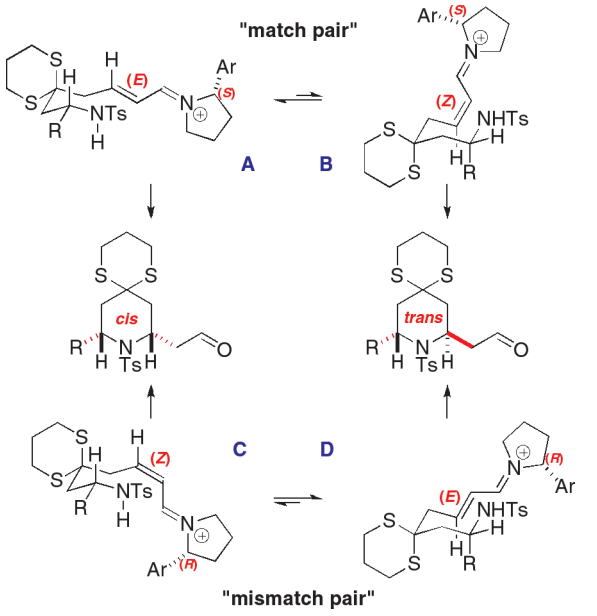


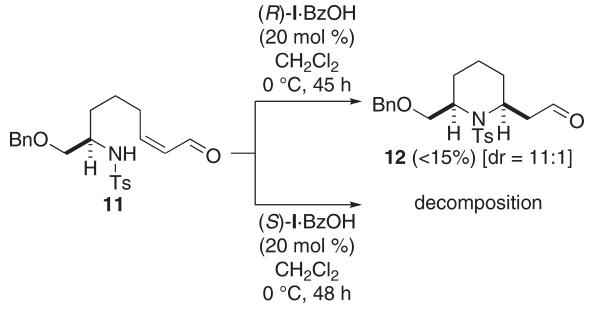
Figure 1. Proposed mechanism of cyclization of (*E*)- and (*Z*)-iminium ions.

The origin of the higher stereoselectivity with (*S*)-**I** relative to (*R*)-**I** can be explained as illustrated in Figure 1. The (*E*)-enal forms a "match pair"[14] with (*S*)-**I** and proceeds through conformer **A** to provide the 2,6-*cis*-piperidine with excellent stereoselectivity. However, the combination of (*R*)-**I** and (*E*)-enal produces a "mismatch pair", which leads to the formation of multiple competing transition states to give 2,6-*trans*-piperidine with lower stereoselectivity (conformer **D**). The reason for the higher stereoselectivity with (*E*)-enals relative to (*Z*)-enals can be rationalized on the basis that while the (*Z*)-iminium ion intermediates undergo a cyclization to provide the corresponding 2,6-*trans*-piperidine (through conformer **B** in "match pair") and 2,6-*cis*-piperidine (through conformer **C** in "mismatch pair"), competitive and rapid isomerization to the corresponding (*E*)-iminium ion intermediates[15] could occur to eventually provide the opposite diastereomers, which results in lower stereoselectivity relative to (*E*)-iminium ion intermediates.

We hypothesized that the 1,3-dithiane group would be critical to overcome the low reactivity of sulfonamides by promoting an ideal conformation for cyclization through the *gem*-disubstituent effect.[16] To test this hypothesis, we prepared substrate **11** with no *gem*-disubstituent effect and

(14) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.
(15) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33.
(16) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

Scheme 3. *gem*-Disubstituent Effect on Stereoselectivity and Reaction Rate

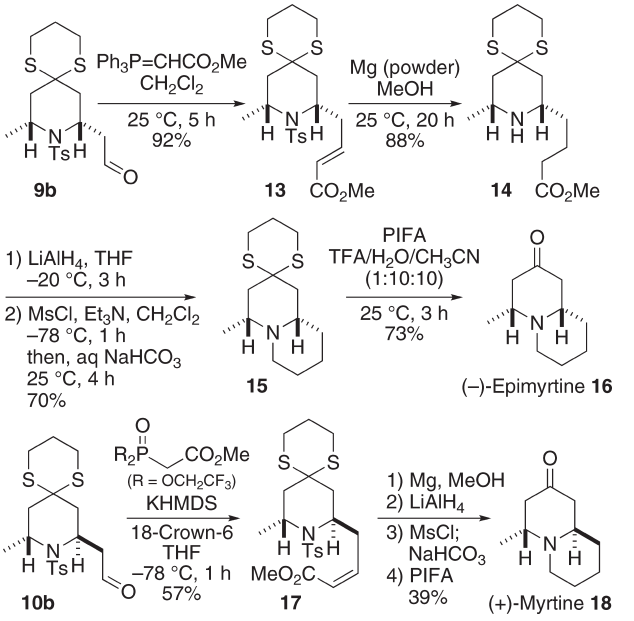


subjected it to the reaction conditions (Scheme 3). Although the organcatalytic aza-Michael reaction of **11** in the presence of (*R*)-**I** provided 2,6-*cis*-piperidine **12** with good stereoselectivity (dr = 11:1), the yield was poor (< 15%). The organocatalytic aza-Michael reaction of **11** in the presence of (*S*)-**I** failed to provide the corresponding 2,6-*trans*-piperidine; instead, decomposition of **11** was observed. These data clearly demonstrate that the *gem*-disubstituent effect by the 1,3-dithiane group is critical to overcoming the poor nucleophilicity of sulfonamides and improving the yield.

To demonstrate the versatility of the organocatalytic aza-Michael reactions for the stereoselective synthesis of 2,6-disubstituted piperidines, we embarked on the facile synthesis of (−)-epimyrtine (**16**) and (+)-myrtine (**18**) (Scheme 4).[17,18] We envisioned that both 2,6-*cis*- and 2,6-*trans*-piperidines embedded in **16** and **18**, respectively, could be constructed from a common substrate using the organocatalytic aza-Michael reactions.

Witting reaction of aldehyde **9b** with methyl (triphenylphosphoranylidene)acetate followed by dissolving metal reduction of the resulting (*E*)-α,*β*-unsaturated ester **13** afforded ester **14** with accompanying deprotection of the Ts group. $LiAlH_4$-reduction, mesylation, and subsequent intramolecular *N*-alkylation provided quinolizidine **15**.

Scheme 4. Synthesis of (−)-Epimyrtine and (+)-Myrtine



Final deprotection of 1,3-dithiane group in **15** in the presence of bis(trifluoroacetoxy)iodo benzene[19] completed the synthesis of (−)-epimyrtine (**16**).

Starting from an inseparable mixture of **10b** and **9b** (4:1), Still−Gennari olefination[20] followed by a separation of the resulting α,*β*-unsaturated esters provided (*Z*)-α,*β*-unsaturated ester **17**. Compound **17** was converted to (+)-myrtine (**18**) following the procedures described above.

In summary, the organocatalytic aza-Michael reaction was explored for the stereoselective synthesis of 2,6-disubstituted piperidines. The organocatalytic aza-Michael reactions allowed the synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from the common substrates. The reaction proceeded with modest to excellent stereoselectivities (up to 20:1 dr) and yields. The 1,3-dithiane group allowed for rapid access to substrates and promoted the intramolecular aza-Michael reaction via the *gem*-disubstituent effect. We also demonstrated the utility of the combination of the organocatalytic aza-Michael reaction and the dithiane coupling reaction in the concise synthesis of (−)-epimyrtine (**16**) and (+)-myrtine (**18**) from the common intermediate. This synthetic method would be broadly applicable to the efficient synthesis of a diverse set of bioactive natural products with 2,6-disubstituted piperidines.

Acknowledgment. This work was supported by Duke University. We are grateful to the NCBC (Grant No. 2008-IDG-1010) for funding of NMR instrumentation.

Supporting Information Available. General experimental procedures including spectroscopic and analytical data along with copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For the isolation of (+)-myrtine and (−)-epimyrtine, see: (a) Slosse, P.; Hootele, C. *Tetrahedron Lett*. **1978**, 397–398. (b) Slosse, P.; Hootele, C. *Tetrahedron* **1981**, *37*, 4287–4294.

(18) For the synthesis of myrtine and epimyrtine, see: (a) Slosse, P.; Hootele, C. *Tetrahedron Lett*. **1979**, *19*, 4587–4588. (b) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 447–453. (c) Comins, D. L.; Brown, J. D. *Tetrahedron Lett*. **1986**, *27*, 4549–4552. (d) Comins, D. L.; Weglarz, M. A.; O'Connor, S. *Tetrahedron Lett*. **1988**, *29*, 1751–1754. (e) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett*. **1989**, *30*, 5053–5056. (f) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem*. **1992**, *57*, 5807–5809. (g) Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett*. **1992**, *33*, 73–76. (h) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett*. **1993**, *34*, 2729–2732. (i) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem*. **1995**, *60*, 717–722. (j) Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1823–1828. (k) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem*. **2003**, *68*, 8061–8064. (l) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem*. **2005**, *70*, 967–972. (m) Amorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett*. **2005**, *7*, 2031–2033. (n) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem*. **2007**, *72*, 2046–2052. (o) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem*. **2008**, *6*, 3464–3466. (p) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222–3231.

(19) (a) Stork, G.; Zhao, K. *Tetrahedron Lett*. **1989**, *30*, 287–290. (b) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem*. **2001**, *66*, 6502–6504.

(20) Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405–4408.