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Synthesis of (±)-Bistellettadine A

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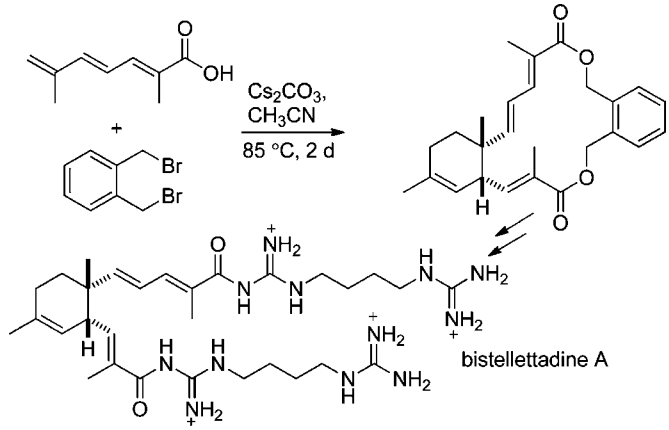
ABSTRACT



Esterification of the trienoic acid with *o*-xylylene dibromide gave the bis ester that underwent a templated Diels−Alder reaction to afford the macrodiolide stereospecifically in a single step. The synthesis of bistellettadine A was completed in four steps by hydrolysis and side chain elaboration.

As part of our continuing interest in the synthesis of guanidine-containing alkaloids, we were intrigued by the biologically active, dimeric, tetra guanidines bistellettadines A (**1a**) and B (**2**), which were recently isolated by Fusetani and co-workers from a *Stelletta* sponge collected from Shikine-jima island, 200 km south of Tokyo (see Figure 1).[1,2] They inhibit Ca^{2+}/calmodulin-dependent phosphodiesterase (40% inhibition at 100 μM) and the growth of yeast and *E. coli* at 10 μg/disk. The structures of the bistellettadines were determined by spectroscopic analysis and the cis relationship of the two unsaturated side chains on the cyclohexene was established by NOE experiments. Bistellettazine A (**3**), a structurally related dimeric marine natural product with trans unsaturated side chains, was isolated by Capon in 2008.[2f] Dimers **1a** and **2** are probably biosynthesized by a Diels−Alder reaction of two monomers analogous to stellettadine A (**7**)[2b] (see Scheme 1). The stereochemistry of the Diels−Alder reaction may be controlled in the biosynthesis. However, closely related bis sesquiterpene dimers have been isolated as mixtures of cis and trans isomers.[3] This raises the possibility that the Diels−Alder reactions are not stereoselective and that the trans isomer **1b** and the cis isomer of **3** were present in the sponges but were not isolated and characterized.

Mori and co-workers synthesized stellettadine A (**7**)[2b] by coupling Boc-protected agmatine **4** and acyl chloride **5** to provide the diacylated product **6** in 62% yield (see Scheme 1).[4] Removal of the Boc group of **6** under acidic conditions

(1) Tsukamoto, S.; Yamashita, T.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1999**, *64*, 3794–3795.

(2) For related compounds isolated from other *Stelletta* sponges, see: (a) Hirota, H.; Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1990**, *31*, 4163–4164. (b) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *Tetrahedron Lett.* **1996**, *37*, 5555–5556. (c) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J. R.; Sim, C. J. *J. Nat. Prod.* **1997**, *60*, 611–613. (d) Matsunaga, S.; Yamashita, T.; Tsukamoto, S.; Fusetani, N. *J. Nat. Prod.* **1999**, *62*, 1202–1204. (e) Tsukamoto, S.; Yamashita, T.; Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1999**, *40*, 737–738. (f) El-Naggar, M.; Piggott, A. M.; Capon, R. J. *Org. Lett.* **2008**, *10*, 4247–4250.

(3) Mao, S.-C.; Manzo, E.; Guo, Y.-W.; Gavagnin, M.; Mollo, E.; Ciavatta, M. L.; van Soest, R.; Cimino, G. *Tetrahedron* **2007**, *63*, 11108–11113.

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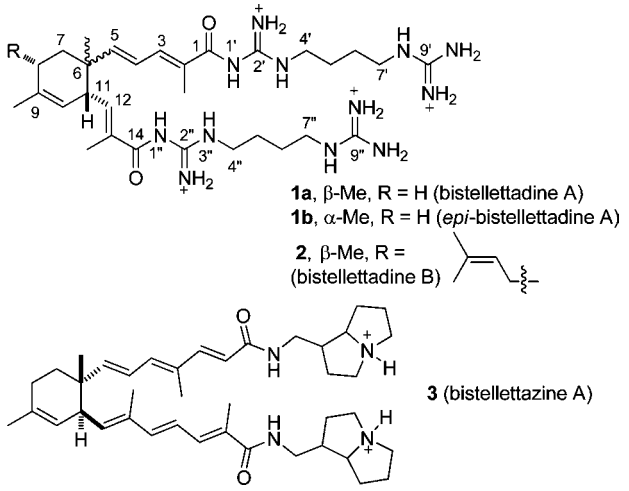
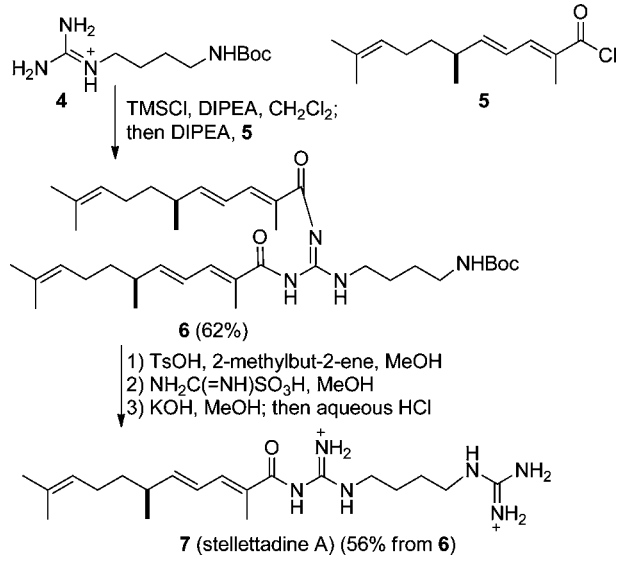


Figure 1. Structures of bistellettadines A (**1a**) and B (**2**), *epi*-bistellettadine A (**1b**), and bistellettazine A (**3**).

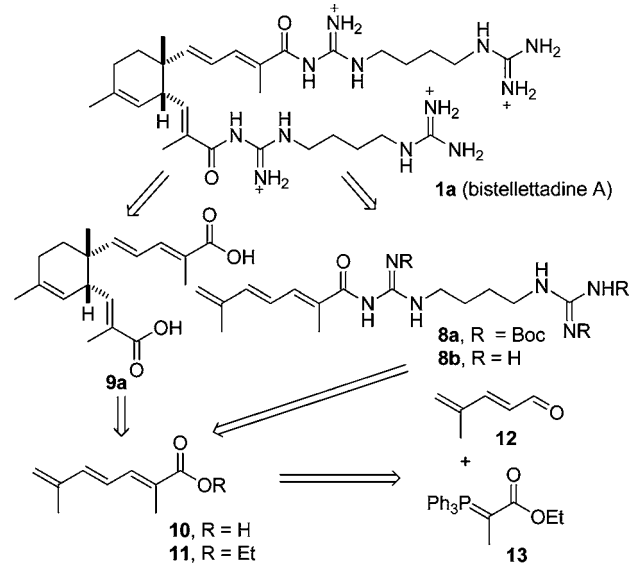
followed by treatment of the resulting amine with aminoiminomethanesulfonic acid constructed the second guanidine group. The extra acyl group was removed using KOH to afford stellettadine A (**7**) in 56% overall yield from **6**. The yield of this four-step sequence is 35% from **4**, but only 17% based on acyl chloride **5**.

Scheme 1. Mori's Synthesis of Stellettadine A (**7**)



Our retrosynthesis analysis of **1a** is shown in Scheme 2. A Diels−Alder dimerization of two molecules of **8a** or **8b** could give **1a** (after deprotection if **8a** is used). Bis guanidine **8a** will be prepared from trienoic acid **10** resulting from the hydrolysis of ester **11** formed by the Wittig reaction of trienal **12**[5] and ylide **13**. Alternatively, the Diels−Alder reaction of **10** or **11** could be carried out before introduction of the guanidine side chains to give diacid **9a**, which will then be elaborated to **1a**. We hoped that the carboxylate salt of **10** might orient in water to give selectively the desired Diels−Alder adduct **9a** with cis unsaturated side chains.[6]

Scheme 2. Retrosynthesis of (±)-Bistellettadine A (**1a**)



Mori's procedure for the introduction of the guanidine side chain of stellettadine A (**7**) that proceeds through a bis acyl guanidine could be used for the conversion of acid **10** to monomer **8b**, but it cannot be used for the conversion of diacid **9a** to **1a**. We therefore needed to develop a more efficient procedure for introduction of the guanidine side chain that does not proceed through a diacylated intermediate analogous to **6**.

Wittig reaction of readily available dienal **12**[5] and ylide **13** was most effectively carried out in THF at 70 °C for 15 min under microwave irradiation to give **11** in 85% yield (see Scheme 3). The unstable trienoate **11** decomposed partially and gave some Diels−Alder dimer at longer reaction times, higher temperatures, or with traditional heating. Hydrolysis of ester **11** with LiOH in 4:2:1 THF/MeOH/H_2O for 16 h followed by neutralization with 6 M HCl gave crude acid **10**. Coupling[7] of acid **10** and **14**[7] in CH_2Cl_2 using DIPEA, EDC, and HOBT gave **15** in 59% overall yield from ester **11**, which was treated with bis Boc-protected agmatine **16**,[8] Et_3N, and $AgNO_3$ in DMF at 0 °C for 3 h and at 25 °C for 4 h to give **8a** in 77% yield as a 2:3 mixture of tautomers. Deprotection of the Boc groups of **8a** using TFA gave the

(4) (a) Takikawa, H.; Nozawa, D.; Mori, K. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 657–661. (b) Nozawa, D.; Takikawa, H.; Mori, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1481–1483.

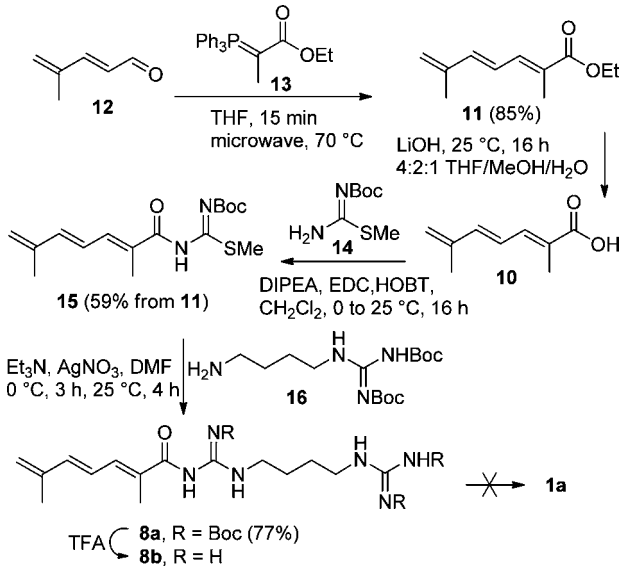
(5) Spangler, C. W.; McCoy, R. K.; Karavakis, A. A. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 1203–1207.

(6) We have previously observed that photochemical [2 + 2] cycloadditions of anchinopeptolide D occurs selectively in water, but not MeOH: Snider, B. B.; Song, F.; Foxman, B. *J. Org. Chem.* **2000**, *65*, 793–800.

(7) Weiss, S.; Keller, M.; Bernhardt, G.; Buschauer, A.; König, B. *Bioorg. Med. Chem.* **2008**, *16*, 9858–9866.

(8) Sarabia, F.; Sánchez-Ruiz, A.; Chammaa, S. *Bioorg. Med. Chem.* **2005**, *13*, 1691–1705.

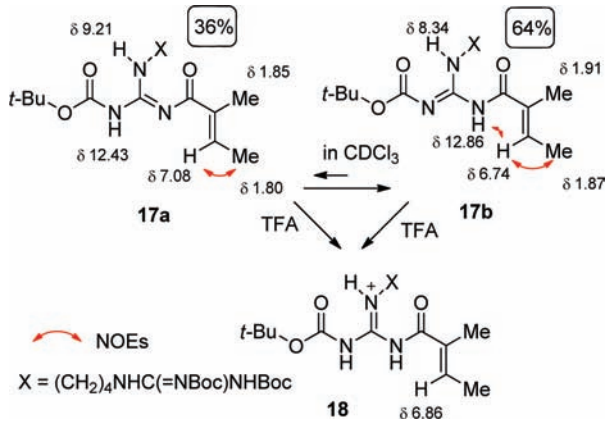
Scheme 3. Unsuccessful Approach to Bistellettadine A (**1a**)



bis trifluoroacetate salt **8b**. Unfortunately, initial attempts to carry out Diels−Alder dimerizations of either **8a** or **8b** resulted in polymerization of the sensitive trienoyl guanidine.

To establish the structures of the two tautomers of **8a**, we prepared an inseparable 36:64 mixture of the simpler tautomers **17a** and **17b** from tiglic acid using the two-step procedure described above for the conversion of **10** to **8a** (see Scheme 4). The alkene proton at δ 7.08 in the minor

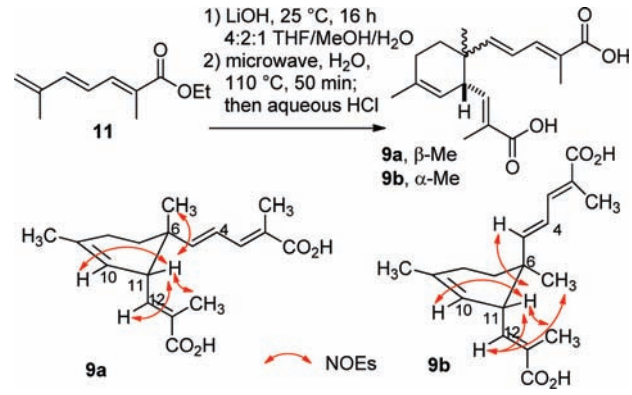
Scheme 4. Model Tautomers **17a** and **17b**



isomer **17a** shows a strong NOE only to the geminal methyl group at δ 1.80. However, the alkene proton at δ 6.74 in the major isomer **17b** shows strong NOEs not only to the geminal methyl group at δ 1.87, but also to the N−H proton at δ 12.86. The presence of both tautomers indicates that the N−H exchange is slow on the NMR time scale.[9] Protonation of both **17a** and **17b** should give the same diacylguanidinium cation. Treatment of the mixture in $CDCl_3$ with TFA gave **18** as a single compound in which the alkene proton absorbed at δ 6.86.

We then investigated the Diels−Alder dimerization of trienoate ester **11** in organic solvents and the lithium salt of trienoic acid **10** in water. Hydrolysis of **11** with LiOH followed by concentration gave the lithium salt, which underwent a clean Diels−Alder dimerization in water under microwave irradiation at 110 °C for 50 min to give an inseparable 5:4 mixture of crude **9a** and **9b** in 94% yield (see Scheme 5). Heating trienoate ester **11** in toluene at 125

Scheme 5. Diels−Alder Dimerization of **11** to Give **9a** and **9b**



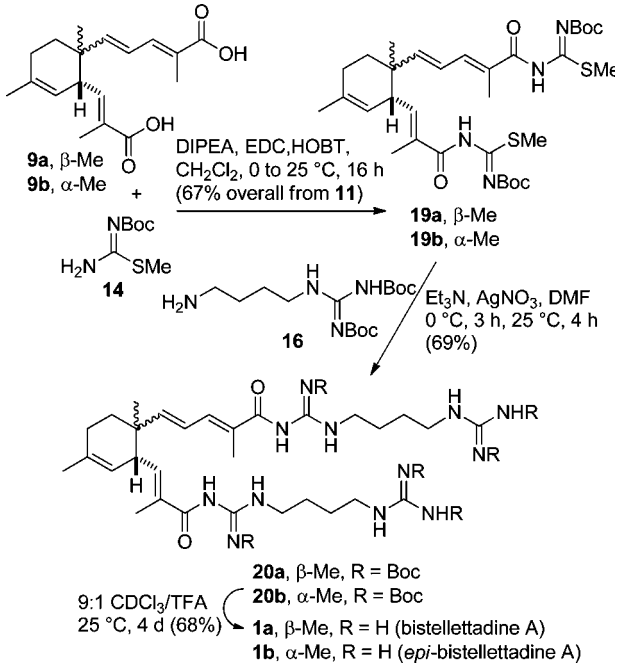
°C for 2 days followed by hydrolysis gave a similar mixture of **9a** and **9b** in comparable yield. An NOE between H-11 and the C-6 methyl group in **9a** suggested that the unsaturated side chains of the major isomer **9a** have the desired cis relationship. NOEs between H-11 and H-5 and between H-12 and the C-6 methyl group established that the unsaturated side chains are trans in the minor isomer **9b**.

Analytical, but not preparative, separation of **9a** and **9b** was achieved on reverse phase silica gel. We therefore coupled the mixture of **9a** and **9b** with **14**, DIPEA, EDC, and HOBT to afford an inseparable 5:4 mixture of **19a** and **19b** in 67% overall yield from trienoate ester **11** (see Scheme 6). Treatment of this mixture with **16**, Et_3N, and $AgNO_3$ in DMF afforded a 5:4 mixture of **20a** and **20b** in 69% yield. Stirring this mixture in 9:1 $CDCl_3$/TFA at 25 °C for 4 days cleaved all six Boc groups to give a 5:4 mixture of **1a** and **1b** in 68% yield as the tetra trifluoroacetate salts, which were readily separated by reverse phase HPLC. The ^1H and ^{13}C NMR spectra of synthetic **1a** in DMSO-d_6 correspond very closely to those of natural **1a**.[1,10] The spectra of **1b** are very similar except that H-11 is shifted downfield by 0.07 ppm to δ 3.14, the C-6 methyl group is shifted upfield by 0.10

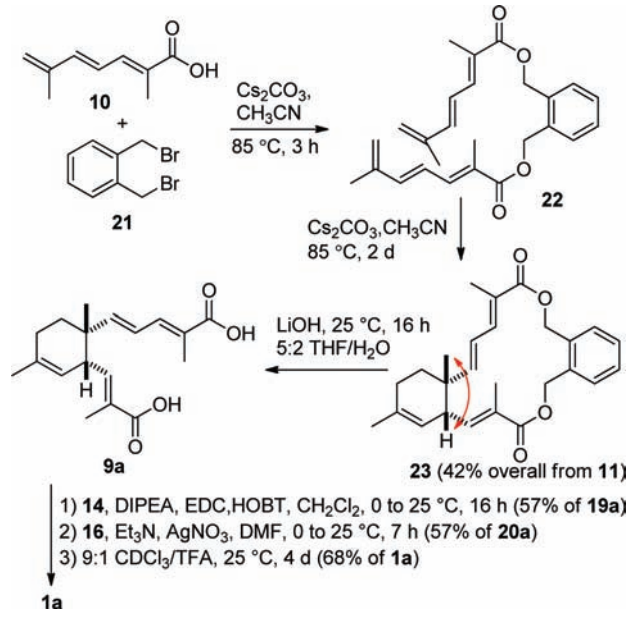
(9) Slow N-H exchange has been observed previously in symmetrical *N*,*N*′-bisacyl guanidines. The acetyl methyl groups of 3-(*N*,*N*′-diacetylguanidino)-3,7-dimethyloctane absorb at δ 2.10 and δ 2.15: Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **1999**, *55*, 4325–4340. The ortho benzoyl protons of *N*,*N*′-dibenzoyl-*N*″-methylguanidine absorb at δ 8.04 and δ 8.30: Newton, C. G.; Ollis, W. D. *J. Chem. Soc., Perkin. Trans. 1* **1984**, 75–84.

(10) The assignments in ref 1 for protons and carbons 2′ to 9′ and 2″ to 9″ appear to be in the wrong order as discussed in more detail in the Supporting Information.

Scheme 6. Completion of Bistellettadine A (**1a**) Synthesis



Scheme 7. Use of Templated Diels−Alder Reaction to Synthesize Bistellettadine (**1a**)



ppm to δ 1.00, C-5 is shifted downfield by 2.7 ppm to δ 153.0 and the C-6 methyl group is shifted upfield by 2.4 ppm to δ 21.7. These shifts are consistent with the upfield shift expected for gauche butane interactions between C-12 and C-5 in **9a** and between C-12 and the C-6 methyl group in **9b**.

Unfortunately, the Diels−Alder dimerization of ester **11** or the salt of acid **10** proceeded cleanly but with poor stereocontrol. Coupling two molecules of acid **10** to a linker by a temporarily tether will form a substrate that can undergo an intramolecular Diels−Alder reaction.[11] The tether needs to be easily attached and removed, long enough to accommodate the different lengths of the unsaturated side chains in the Diels−Alder adduct, and yet short enough to facilitate an intramolecular Diels−Alder reaction and favor the formation of the isomer with cis unsaturated side chains. Molecular mechanics calculations suggested that the intramolecular Diels−Alder reaction of **22** should give **23** stereospecifically.[12] We therefore treated acid **10** (2.5−4 equiv) with *o*-xylylene dibromide (**21**) and Cs_2CO_3 in CH_3CN at 85 °C (see Scheme 7). After 3 h, **21** was completely converted to bis ester **22** and ∼10% of Diels−Alder product **23** had already formed. Heating for 2 days gave exclusively macrodiolide **23** with the cis configuration of the unsaturated side chains in 42% overall yield from **11** (80% yield from **21**). Remarkably, the intramolecular Diels−Alder reaction proceeded stereospecifically under milder conditions than the intermolecular Diels−Alder dimerization of **10** or **11** to form **23** with a 16-membered ring macrodiolide. The stereochemistry of **23** was established by NOEs between H-11 and the C-6 methyl group. Hydrolysis of **23** using LiOH in 5:2 THF/H_2O at 25 °C for 16 h gave **9a**. Coupling of **9a** with **14** gave **19a** in 57% overall yield from **23**. Reaction of **19a** with **16** gave **20a** in 57% yield, which was deprotected using TFA for 4 days to give **1a** as a single isomer in 68% yield.

In conclusion, trienal **12** has been converted to bistellettadine A (**1a**) in seven steps in 8% overall yield. Remarkably, the templated Diels−Alder reaction of **22** afforded macrodiolide **23** in excellent yield with complete stereocontrol.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for support of this work. The 800 MHz spectrometer in the Landsman Research Facility, Brandeis University was purchased under NIH RR High-End Instrumentation program, 1S10RR017269-01.

Supporting Information Available: Complete experimental procedures, tables comparing the spectral data of synthetic and natural products, and copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Cox, L. R.; Ley, S. V. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 275−390. (b) Craig, D.; Ford, M. J.; Gordon, R. S.; Stones, J. A.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1999**, *55*, 15045–15066. (c) Craig, D.; Gordon, R. S. *Tetrahedron* **1998**, *39*, 8337–8340. (d) Craig, D.; Ford, M. J.; Stones, J. A. *Tetrahedron Lett.* **1996**, *37*, 535–538.

(12) MMX calculations using PCMODEL 8.0 (Serena Software: Bloomington, IN) indicated that **23** is >3 kcal/mol more stable than the stereoisomer. Transition state calculations also indicated that the transition state leading to **23** was more stable than that leading to the stereoisomer by >3 kcal/mol.