ORGANIC LETTERS

2006
Vol. 8, No. 7
1283−1286

Synthesis of (+)-Sch 642305 by a Biomimetic Transannular Michael Reaction

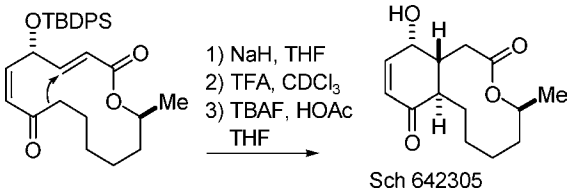
Barry B. Snider* and Jingye Zhou

Department of Chemistry, MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

snider@brandeis.edu

Received December 5, 2005

ABSTRACT

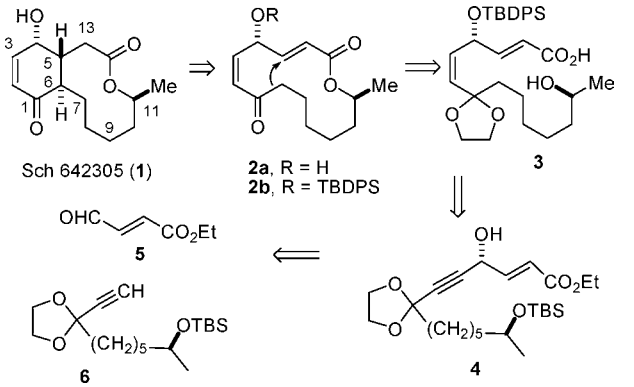


The synthesis of (+)-Sch 642305 (1) has been completed in 17 steps in 1.6% overall yield. Transannular Michael reaction of 2b with NaH in THF provided cyclohexenone 23 stereospecifically. Heating 23 in TFA/$CDCl_3$ provided a 3:1 equilibrium mixture of 23 and 25, which was hydrolyzed to give (+)-6-*epi*-Sch 642305 (24) and (+)-Sch 642305 (1), respectively.

In late 2003, Schering-Plough scientists reported the isolation and structure elucidation of the bicyclic macrolide Sch 642305 (**1**) from *Penicillium verrucosum* (culture ILF-16214) isolated from soil collected near Tucson, AZ.[1] The structure was determined spectroscopically and the absolute stereochemistry was assigned by X-ray crystallographic analysis of the *p*-bromobenzoate ester. Macrolide **1** inhibits bacterial DNA primase with an EC_{50} value of 70 μM.[1] In 2005, Merck scientists reported the isolation of **1** from the fungus *Septofusidium* sp. (JP3241) isolated from leaf litter collected in Puerto Rico.[2] Macrolide **1** inhibits HIV-1 Tat, a regulatory protein required for viral replication, with an IC_{50} value of 1 μM.[2] Mehta and Shinde recently reported the syntheses of (+)-Sch 642305 (**1**)[3] and (+)-11-*epi*-Sch 642305[4] using a ring-closing metathesis to elaborate a 10-membered ring lactone onto a highly functionalized cyclohexene.[5]

We thought that Sch 642305 (**1**) might be biosynthesized by a transannular Michael reaction of the stereochemically simpler hydroxyenone **2a** (see Scheme 1). The close relationship of the macrolides nigrosporolide (**7**)[6] and mutolide (**8**)[7] to the hypothetical biosynthetic intermediate **2a** supports this hypothesis (see Figure 1). If **1** is biosynthesized this way,

Scheme 1. Retrosynthesis of Sch 642305 (**1**)



(1) Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Gullo, V.; Black, T.; Zhao, W.; Chan, T.-M.; McPhail, A. T. *J. Nat. Prod.* **2003**, *66*, 1527−1530.

(2) Jayasuriya, H.; Zink, D. L.; Polishook, J. D.; Bills, G. F.; Dombrowski, A. W.; Genilloud, O.; Pelaez, F. F.; Herranz, L.; Quamina, D.; Lingham, R. B.; Danzeizen, R.; Graham, P. L.; Tomassini, J. E.; Singh, S. B. *Chem. Biodiversity* **2005**, *2*, 112−122.

(3) Mehta, G.; Shinde, H. M. *Chem. Commun.* **2005**, 3703−3705.

(4) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2005**, *46*, 6633−6636.

10.1021/ol052948+ CCC: $33.50
Published on Web 03/04/2006

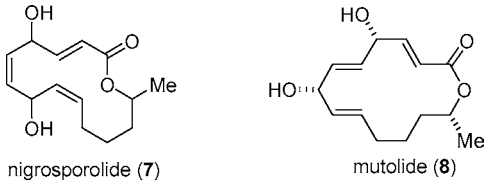


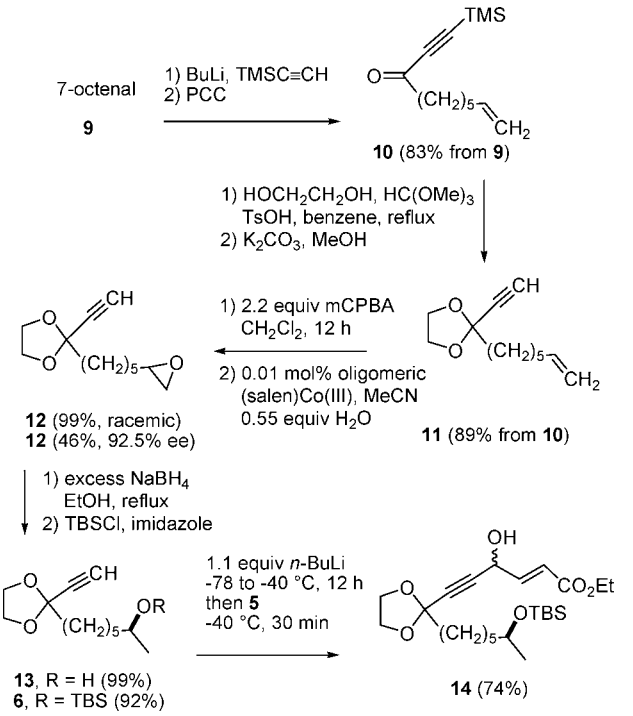
Figure 1. Structures of nigrosporolide (**7**) and mutolide (**8**).

it might also be possible to synthesize it selectively by cyclization of **2a** or a protected derivative such as **2b**. The cyclization of **2** to **1** introduces two new stereocenters so that four isomers are possible. However, related macrolides are often fairly rigid with their conformation controlling the stereochemistry of reactions.[8] Although there are a few reports of synthetic applications of transannular Michael[9] and aldol[10] reactions, the potential of these reactions has not been fully developed.

Macrolide **2** should be readily available by macrolactonization of hydroxy acid **3**, followed by hydrolysis of the dioxolane. Hydroxy acid **3** can be prepared by Lindlar reduction of the alkyne of hydroxy ester **4** followed by protecting group modification. Addition of the acetylide anion formed by deprotonation of **6** to commercially available aldehyde **5** will provide **4** with the complete carbon skeleton of **1**.

Addition of LiC≡CTMS to 7-octenal (**9**)[11] in THF at −40 °C for 2 h afforded the propargylic alcohol, which was oxidized with PCC in CH_2Cl_2 for 12 h to give ynone **10** in 83% overall yield (see Scheme 2). Formation of the dioxolane with $HOCH_2CH_2OH$, $HC(OMe)_3$, and TsOH in benzene at reflux for 8 h, followed by cleavage of the TMS group with K_2CO_3 in MeOH for 12 h at 25 °C, afforded **11** in 89% yield. Epoxidation of the terminal double bond of **11** proceeded cleanly with 2 equiv of mCPBA in CH_2Cl_2 for 12 h. 2-Methyl-2-butene was added and reaction was continued for 4 h to consume excess mCPBA, giving racemic **12** in 99% yield. Jacobsen kinetic resolution[12] using 0.01 mol % of the oligomeric (salen)Co(III) catalyst[13] prepared from the (*R*,*R*)-diamine and 0.5 equiv of H_2O in MeCN for

Scheme 2. Synthesis of **14**



48 h afforded 46% of (*R*)-**12** in 92.5% ee, as determined by chiral HPLC analysis of the 2-mercaptobenzothiazole derivative.[12b] Reduction of the epoxide with $NaBH_4$ in EtOH at reflux for 8 h afforded (*S*)-**13** in 99% yield.[14]

Initially, we had carried out the kinetic resolution of **12** with 1 mol % of the monomeric (salen)Co(II) catalyst and 4 mol % of HOAc, which gave **12** in 43% yield and 97% ee. Reduction of this material with $NaBH_4$ in EtOH for 4 h at 50 °C afforded a 3:1 mixture of **13** and the corresponding alkenol resulting from partial reduction of the triple bond. This byproduct was not formed during reduction of racemic **12**. We speculated that cobalt impurities present even in chromatographically purified, kinetically resolved **12** reacted with $NaBH_4$ to form a catalyst that reduced the triple bond.[15] This was confirmed by reaction of 1-pentadecyne with 1 mol % of monomeric (salen)Co(II) catalyst and excess $NaBH_4$ in EtOH at 55 °C to afford 15% of 1-pentadecene. Under these conditions, 1-octyn-3-ol was reduced more rapidly to give mainly 1-octen-3-ol. This side reaction is minimized with the oligomeric (salen)Co(III) catalyst, which can be used at only 0.01 mol % loading.

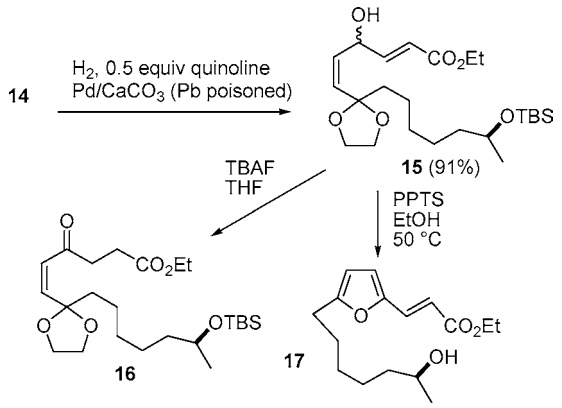
The alcohol of **13** was protected as the TBS ether with TBSCl and imidazole in DMF for 12 h at 25 °C to give **6** in 92% yield. Deprotonation of **6** with *n*-BuLi in THF at −40 °C for 12 h followed by addition of aldehyde **5** and stirring for 30 min at −40 °C gave 74% of **14** as an inseparable 1:1

(5) The numbering scheme used in ref 1 is retained for clarity.
(6) Harwood, J. S.; Cutler, H. G.; Jacyno, J. M. *Nat. Prod. Lett.* **1995**, *6*, 181−185.
(7) Bode, H. B.; Walker, M.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 1451−1456.
(8) Kaisalo, L.; Hase, T. *Synthesis* **2001**, 1619−1622.
(9) (a) Shimizu, I.; Nakagawa, H. *Tetrahedron Lett.* **1992**, *33*, 4957−4958. (b) Matsuura, T.; Yamamura, S. *Tetrahedron Lett.* **2000**, *41*, 4805−4809.
(10) Karim, M. R.; Sampson, P. *Tetrahedron Lett.* **1988**, *29*, 6897−6900.
(11) Prepared in 84% yield by PCC oxidation of the commercially available alcohol.
(12) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315. (c) Ready, J. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1374−1377. (d) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360−1362.
(13) White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633−3638. Catalyst **2a** was used.
(14) For the preparation of analogous alcohols, see: (a) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779−793. (b) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990−7995. Lower yields of **13** were obtained with $LiBEt_3H$.
(15) (a) Chung, S.-K. *J. Org. Chem.* **1979**, *44*, 1014−1016. (b) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801−6802. (c) Satyanarayana, N.; Periasamy, M. *Tetrahedron Lett.* **1984**, *25*, 2501−2504.

mixture of diastereomers. Numerous asymmetric additions of acetylide anions to aldehydes have been reported recently including those of Carriera,[16] Pu,[17] and Shibasaki.[18] In our hands, these procedures worked well on the reported substrates but not with alkyne **6** and aldehyde **5**. We also oxidized **14** to give an enynone and investigated CBS-catalyzed asymmetric reduction,[19] which has been used extensively on enynones. However, the reduction proceeded in only 30−60% yield with up to 70% ee. We therefore continued with **14** as a diastereomeric mixture of isomers, with the expectation that they would be readily separated after formation of the macrolide. The rationale for our approach to **1** was that the conformation and reactivity of macrolide **2** would be controlled by the stereochemistry of the substituents. In a sense, the mixture of diastereomers of **14** is advantageous because it should allow us to easily investigate the transannular Michael reaction of both **2** and its diastereomer.

Hydrogenation of the triple bond of **14** over 5% Pd poisoned with lead (1 mol %) in EtOAc containing 0.5 equiv of quinoline under 1 atm H_2 for 6 h gave alkene **15** in 91% yield (see Scheme 3). The seven adjacent functionalized

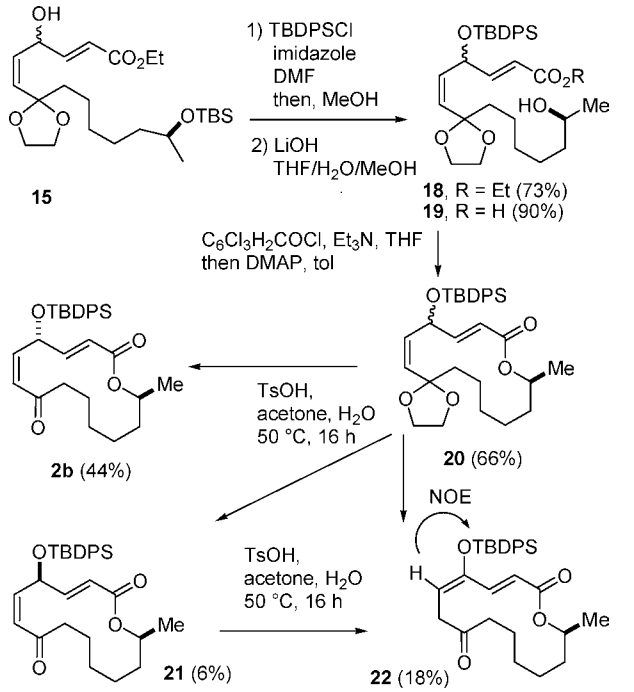
Scheme 3



carbons in **15** made progress toward the macrolide challenge. For instance, treatment with TBAF in THF isomerized the allylic alcohol to give ketone **16**. Cleavage of the TBS ether with PPTS in EtOH at 50 °C also cleaved the dioxolane giving a γ-hydroxy-*cis*-enone that cyclized and lost water to give furan **17**. Hydrolysis of the TBS ether with pyr/HF gave a diol, which underwent basic hydrolysis with LiOH to give the desired dihydroxy acid. However, attempted macrolactonization under Yamaguchi conditions with $C_6H_2Cl_3COCl$, Et_3N, and DMAP failed; the conjugated doubly allylic alcohol is not stable under the reaction conditions. We hoped that protecting the doubly allylic alcohol with a bulky TBDPS ether would allow the macrolactonization to proceed successfully.

Reaction of **15** with excess TBDPSCl and imidazole in DMF for 12 h formed the TBDPS ether. MeOH was added and the solution was stirred for 4 h resulting in cleavage of the TBS ether to give **18** in 73% yield (see Scheme 4). Either

Scheme 4. Preparation of Keto Lactone **2b**



imidazolium chloride or the HCl generated by reaction of excess TBDPSCl with MeOH catalyzed the hydrolysis of the TBS ether without cleaving the dioxolane. Hydrolysis of the ethyl ester with excess LiOH in 2:1:1 THF/MeOH/H_2O for 20 h at 25 °C provided carboxylic acid **19** in 90% yield. Yamaguchi lactonization was effected by slow addition of the mixed anhydride (formed with $C_6H_2Cl_3COCl$ and Et_3N) to DMAP in toluene at 25 °C to give **20** as a difficultly separable mixture of diastereomers in 66% yield. Heating **20** with catalytic TsOH in 10:1 acetone/H_2O at 50 °C for 16 h cleaved the dioxolane to give a readily separable mixture of the desired keto lactone **2b** (44%, 88% from the desired diastereomer of **20**), the diastereomeric ketone lactone **21** (6%, 12% from the undesired diastereomer of **20**), and the isomerized lactone **22** (18%). The stereochemistry of **2b** was assigned by its eventual conversion to **1**. The stereochemistry of the enol ether double bond of **22** was established by an NOE between the alkene and phenyl protons.

Pure macrolide **21** is readily isomerized to **22** by TsOH in acetone/H_2O at 50 °C, whereas the desired isomer **2b** is stable. The stereochemistry of the OTBDPS group has a

(16) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (b) Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233−4236.

(17) Pu, L. *Tetrahedron* **2003**, *59*, 9873−9886.

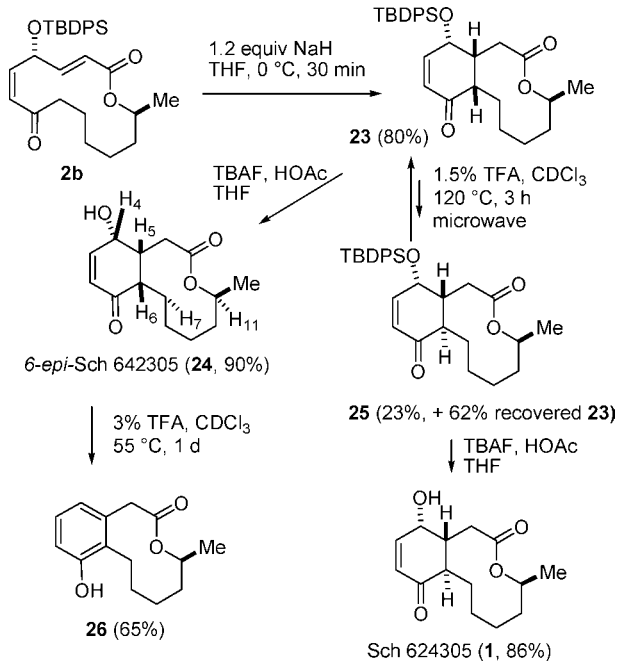
(18) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760−13761.

(19) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309. (c) Garcia, J.; López, M.; Romeu, J. *Synlett* **1999**, 429−431. (d) Yun, H.; Danishefsky, S. J. *J. Org. Chem.* **2003**, *68*, 4519−4522. (e) Parker, K. A.; Katsoulis, I. A. *Org. Lett.* **2004**, *6*, 1413−1416. (f) Garcia, J.; López, M.; Romeu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2617−2626.

profound effect on the stability of **2b** and **21**. Enol formation from **21** is more rapid, suggesting that conformers in which the doubly allylic hydrogen is properly aligned with the enone double bond are more accessible for **21** than for **2b**.

Treatment of **2b** with 1.2 equiv of NaH in THF at 0 °C for 30 min afforded the transannular Michael adduct **23** as a single isomer in 80% yield (see Scheme 5). Deprotection

Scheme 5. Preparation of Sch 642305 (**1**)



of **23** with 1:1 TBAF/HOAc[3] in THF for 3 h at 25 °C provided (+)-6-*epi*-Sch 642305 (**24**) in 90% yield. The cis stereochemistry of **24** was tentatively assigned on the basis of the 3.2 Hz coupling constant between H_5 and H_6. An NOE between H_4 and H_6 completed the assignment of the cyclohexene stereochemistry. An NOE between H_{11} and the H_7 that is antiperiplanar to H_6 suggested that the relative stereochemistry at C_4, C_5, and C_{11} is the same as that in Sch 642305 (**1**). Cyclization of **2b** under a variety of other basic conditions gave predominantly **23** in lower yields. Attempted formation of the silyl enol ether from **2b** led mainly to **22**. Hydrolysis of **2b** with HF/pyr cleaved the silyl ether to give alcohol **2a**, which gave complex mixtures on treatment with base.

6-*epi*-Sch 642305 (**24**) differs from **1** in the stereochemistry at C_6, which is adjacent to a ketone and therefore epimerizable. We were hopeful because MM2 calculations suggested that **1** was about 1 kcal/mol more stable than **24**. Treatment of **24** under basic conditions resulted in no reaction or decomposition. Treatment of **24** with 3% TFA in $CDCl_3$ for 1 day at 55 °C effected dehydration to give only phenol **26** in 65% yield. Treatment of **24** under less acidic conditions with 0.4% TFA in $CDCl_3$ for 14 days at 55 °C gave an inseparable 1.5:1:2 mixture of **24**, **1**, and **26**, respectively. Formation of phenol **26** was minimized by carrying out the isomerization on TBDPS ether **23**. The best results were obtained by microwave irradiation of **23** in 1.5% TFA in $CDCl_3$ for 3 h at 120 °C, which gave a readily separable 1:3 mixture of **25** (23% isolated, 58% based on recovered **23**) and **23** (60% isolated) containing only a trace of phenol **26**. Similar mixtures are obtained starting with **25**, indicating that this is an equilibrium mixture.[20] The spectral data of **25** are identical to those reported by Mehta.[3] Hydrolysis of the TBDPS ether of **25** with TBAF/HOAc[3] in THF afforded (+)-Sch 642305 (**1**) in 86% yield with ^1H and ^{13}C NMR spectral data identical to those previously reported.[1,3]

The carbons at δ 18.5, 22.6, 23.0, and 23.2 are broadened in the ^{13}C NMR spectrum of **24**, and one absorbs as a poorly defined broad peak from δ 29.6 to 30.8 suggesting that a conformational equilibrium is slow on the NMR time scale. This was confirmed by a ^{13}C NMR spectrum of **24** at 50 °C that showed sharp peaks. This broadening is similar, but less pronounced, in the ^{13}C NMR spectrum of **1** at 25 °C.

In conclusion, we have completed the synthesis of (+)-Sch 642305 (**1**) in 17 steps in 1.6% overall yield. Transannular Michael reaction of **2b** with NaH in THF afforded cyclohexenone **23** stereospecifically. TFA-catalyzed equilibration provided a 3:1 mixture of **23** and **25**, which was hydrolyzed to give (+)-6-*epi*-Sch 642305 (**24**) and (+)-Sch 642305 (**1**), respectively.

Acknowledgment. We thank the NIH (GM50151) for generous financial support. We thank Prof. Eric Jacobsen for a sample of the oligomeric (salen)Co(III) catalyst.

Note Added in Proof: While this paper was under review, another synthesis of Sch 642305 was reported. See: Ishigami, K.; Katsuta, R.; Watanabe, H. *Tetrahedron* **2006**, *62*, 2224−2230.

Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052948+

(20) Although MM2 calculations suggested that **25** is about 1 kcal/mol more stable than **23**, the equilibration studies indicate that it is less stable. This could be due to inaccuracies in the MM2 calculations or entropic effects.