ORGANIC LETTERS

2006
Vol. 8, No. 17
3849−3851

A Tether Controlled *exo*-Selective Trans-Annular Diels–Alder (TADA) Reaction†

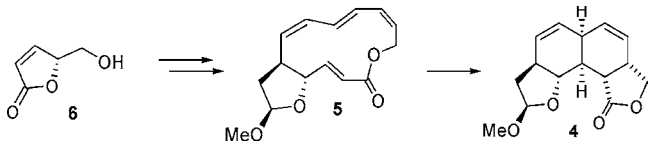
Wolfgang Felzmann,§ Vladimir B. Arion,‡ Jean-Luc Mieusset,§ and Johann Mulzer*,§

Institut für Organische Chemie, Universität Wien, Währingerstrasse 38, A-1090 Vienna, Austria, and Institut für Anorganische Chemie, Universität Wien, Währingerstrasse 42, A-1090 Vienna, Austria

johann.mulzer@univie.ac.at

Received June 20, 2006

ABSTRACT



A fully substrate controlled stereoselective route to construct *cis*-hexahydronaphthalene 4 is described starting from nonracemic butenolide 6. The key step is an *exo*-selective transannular Diels–Alder reaction (TADA) of tetraene 5, whose intrinsic constraint allows selective formation of one stereodefined product. Compound 4 is a key intermediate in the synthesis of the novel antibiotic branimycin (1).

Transannular Diels−Alder (TADA) reactions[1] have repeatedly proven their value in the construction of bicyclo[4.3.0]-nonane and bicyclo[4.4.0]decane systems present in natural products. In the overwhelming majority of cases, these reactions proceed via *endo* transition states.[1] We were intrigued by the idea to overrule this intrinsic preference by a suitable conformational constraint so that the *exo*-transition state would instead be favored.[2] This concept gained momentum when we embarked on a total synthesis of branimycin (**1**),[3] a novel antibiotic that has been isolated from *Streptomyces* by the Laatsch group.[4] Structurally, **1** belongs to the nargenicin-type antibiotics such as nodusmycin (**2a**) and the nargenicins (**2b**,**c**)[5] which have been the object of intensive synthetic efforts over the past twenty years (Figure 1).[6,7] Despite this, only the synthesis of **2c** has been completed so far.[6]

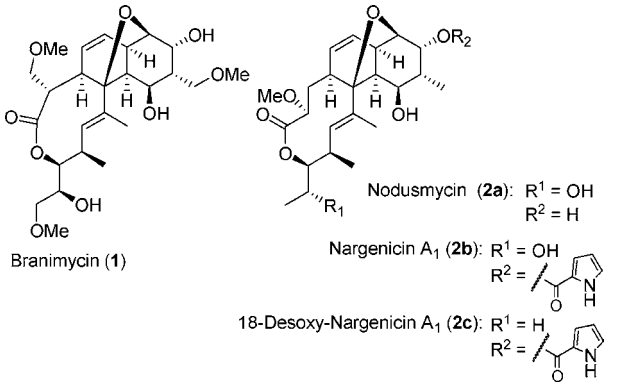


Figure 1. Branimycin and related nargenicins.

Our retrosynthetic concept envisaged the synthesis of the octahydronaphthalene core (**3**) of branimycin (**1**) via Diels−

† This paper is dedicated to Prof. Bernhard Kräutler on occasion of his 60th birthday.

§ Institut of Organic Chemistry.

‡ Insitute of Inorganic Chemistry.

(1) For reviews on TADA reactions, see: (a) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779 and references therein. (b) Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243 and references therein.

(2) An example showing low selectivity has been reported: Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 553.

(3) Enev, V. S.; Drescher, M.; Kaehlig, H.; Mulzer, J. *Synlett* **2005**, *14*, 2227.

(4) Speitling, M. Ph.D. Thesis, Universität Göttingen, 1998.

10.1021/ol061510m CCC: $33.50
Published on Web 07/21/2006

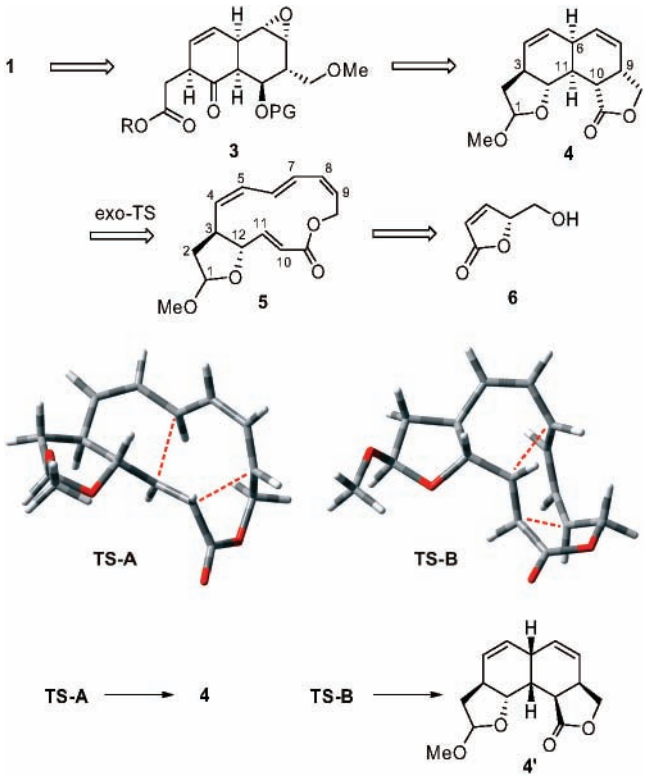
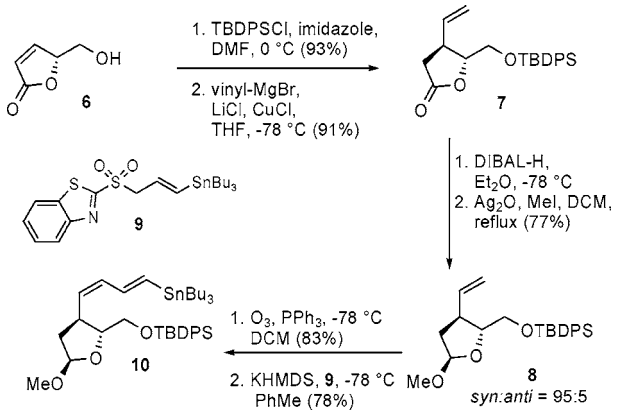


Figure 2. Retrosynthesis and transition state calculations: for **TS-A**, C11−C6 = 243.7 pm and C10−C9 = 214.5 pm; for **TS-B**, C11−C6 = 251.5 pm and C10−C9 = 210.8 pm.

Alder cycloaddition (Figure 2). Early studies had shown that an open-chain *Z,E,Z*-trienol was unstable under various IMDA conditions. Therefore, a TADA version under substrate control showed the highest promise to perform this reaction with optimal stereocontrol. This led us to intermediate **4** as this compound could be constructed by a TADA reaction from macrolide **5**. To obtain the correct relative configurations at C6, C9, C10, and C11 the macrolide must have a 6,7-*E*-8,9-*Z*-10,11-*E*-configuration. The absolute configuration can be induced by the chiral tether, for which we chose a lactol ring. On the basis of molecular model inspections we found that a cis-fused lactol at C3/C12 is too flexible for a stereocontrolled cyclization. In the trans-fused system, however, *endo*-geometries are strained, where only the two *exo*-transition states **TS-A** (leading to **4**) and **TS-B** (leading to **4′**) can be adopted. DFT calculations (B3LYP/6-31G(d)) predicted a better conjugation of the diene unit and a lower energy difference between HOMO and LUMO in the reactants of **TS-A**, making it 2.5 kcal/mol lower in energy than **TS-B**. Hence, **4** was expected to be formed with high selectivity. However, it was an open question how such a highly unsaturated macrocycle as **5** can be constructed and if the (*Z*)-double bonds would survive the Diels−Alder conditions, to yield the desired cis-fused hexahydronaphthalene ring.[8] Additionally, the behavior of *Z,E,Z*-trienol derivatives as diene substrates in Diels−Alder reactions is unknown and, as already mentioned, *exo*-transition states are uncommon in TADA reactions. On this background, our project promised novel insight into such transformations,[9] all the more so as the Roush group reported a related TADA example in which a *cis*-octahydronaphthalene is formed via an *endo* transition state. [7a]

The synthesis of macrolide **5** was started from known butenolide **6**,[10] which was protected as the TBDPS-ether (Scheme 1). Vinyl-1,4-addition was found to proceed

Scheme 1. Synthesis of *E,Z*-Diene **10**



smoothly by using catalytic amounts of CuCl/LiCl at −78 °C. As lactone **7** proved incompatible with the subsequent reaction conditions, it was reduced immediately with DIBAL-H and converted to the methyl lactol **8** with Ag_2O

(5) (a) For a review see: Kallmerten, J. *Studies in Natural Products Chemistry;* Elsevier: Amsterdam, The Netherlands, 1995; Vol. 17, pp 283−310 and cited literature. (b) Nargenicin: Celmer, W. D.; Chmurny, C. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203. (c) See also: Tone, J.; Shibakawa, R.; Maeda, H.; Yamauchi, Y.; Niki, K.; Saito, M.; Tsukuda, K.; Whipple, E. B.; Watts, P. C.; Moppett, C. E.; Jefferson, M. T.; Huang, L. H.; Cullen, W. P.; Celmer, W. D. *20th Interscience Conference on Antimicrobial Agents and Chemotherapeutics*; New Orleans, LA, 1980, pp 22−24. (d) Nodusmycin: Whaley, H. A.; Chidester, C. G.; Mizak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659. (e) See further: Whaley, H. A.; Coates, J. H. *21st Interscience Conference on Antimicrobial Agents and Chemotherapeutics*, Chicago, IL, 1981, Abstract 187.

(6) Total synthesis of **2c**: (a) Plata, D. J.; Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041. (b) Kallmerten, J.; Plata, D. J. *Heterocycles* **1987**, *25*, 145. (c) Rossano, L. T.; Plata, D. J.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 5189.

(7) (a) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. (b) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (c) Roush, W. R.; Coe J. W. *Tetrahedron Lett.* **1987**, *28*, 931. (d) Gössinger, E.; Schwartz, A.; Sereinig, N. *Tetrahedron* **2001**, *57*, 3045 and references therein.

(8) For a review on *cis*-decalins see: Singh, V.; Iyer, S. R.; Pal, S. *Tetrahedron* **2005**, *61*, 9197 and references therein.

(9) For Diels−Alder reactions of decatrienones, see: (a) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1355. (b) Kim, K.; Maharoof, U. S. M.; Raushel, J.; Sulikowski, G. A. *Org. Lett.* **2003**, *5*, 2777. (c) Miyaoka, H.; Shida, H.; Yamada, N.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2002**, *43*, 2227. (d) Taber, D. F.; Nakajima, K.; Xu, M.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 4501. (e) Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 2793. (f) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989.

(10) (a) Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2976. (b) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403.

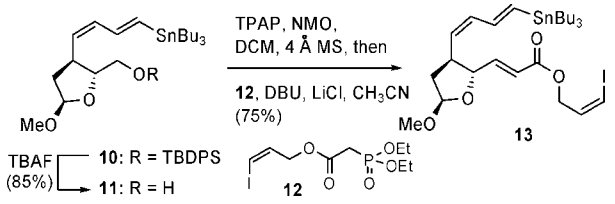
and MeI[11] in refluxing CH_2Cl_2 (70% over 3 steps, *syn*:*anti* ≥ 95:5).

After ozonolysis of **8**, the installation of the desired (*E*,*Z*)-diene could be most effectively accomplished by using a (*Z*)-selective, modified Julia-olefination with sulfone **9**,[12] which yielded **10** in 60% yield and a *Z*,*E*:*E*,*E*-selectivity of 85:15.

As preliminary experiments had shown that an open-chain *Z*,*E*,*Z*-triene obtained from intermolecular Stille coupling of **10** with phosphonate **12** was prone to isomerization, we decided to construct this delicate part of the molecule as late as possible. We therefore decided to build the triene as the last step in an intramolecular Stille-coupling to form macrocycle **5**.

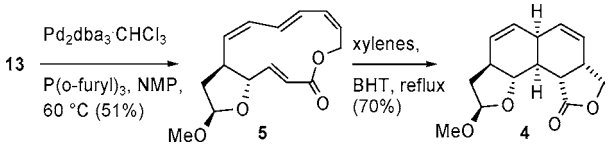
After TBDPS-cleavage, alcohol **11** could only be converted to the α,β-unsaturated ester **13** by using a TPAP-oxidation/Roush−Masamune olefination sequence as the intermediate aldehyde turned out to be highly unstable. By using phosphonate **12** under these conditions, *seco*-compound **13** could be obtained in acceptable 75% yield (Scheme 2).

Scheme 2. Synthesis of *seco*-Compound **13**



Intramolecular Stille-coupling[13] under high-dilution conditions gave the desired macrocyclic tetraene **5** in 51% isolated yield (Scheme 3). The TADA reaction of tetraene **5** under

Scheme 3. Coupling and TADA Reaction of **13**



thermal conditions (140 °C, 24 h) yielded **4** as a single diastereomer in 70% yield.[14] Its structure was determined on the basis of extensive NOE studies and also by single-crystal diffraction.[14]

The MM-model and the solid-state conformation are fully superimposable, thus demonstrating the rigidity of the polycyclic template. The two cyclohexene moieties adopt half-chair envelope-like geometries with planes nearly perpendicular to each other (Figure 3).

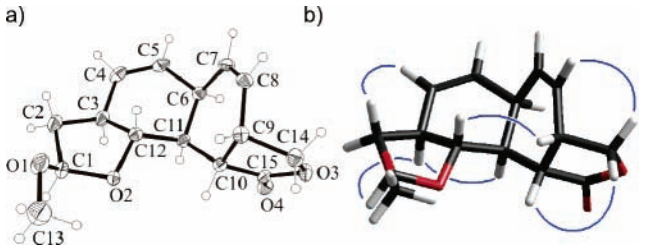


Figure 3. (a) ORTEP projection (ellipsoids: 50% probability) of TADA product **4** and (b) observed NOE interactions on a molecular mechanics model.

In conclusion, we have demonstrated that the TADA reaction of macrolide **5** prefers an *exo*-transition state. The overall sequence, starting from lactone **6**, establishes 6 new stereogenic centers in 11 linear steps via purely substrate controlled transformations. We are currently exploiting this approach to finalize the total synthesis of branimycin, which will be reported in due course.

Acknowledgment. We thank Schering AG for a generous gift of chemicals. Valentin Enev and Neil A. Sheddan are acknowledged for helpful discussion (University of Vienna). We are also grateful to Hanspeter Kählig for NMR (University of Vienna)

Supporting Information Available: Cartesian coordinates for transition and ground states; experimental details and characterization data for compounds **4**, **5**, **7**, **8**, **10**, **11**, **12**, **13**, and **14**, as well as crystallographic data for **4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL061510M

(11) (a) Nicolaou, K. C.; Snyder, S. A.; Huang, X.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.* **2004**, *126*, 10162. (b) Yoda, Y.; Nakaseko, K.; Takabe *Tetrahedron Lett.* **2004**, *45*, 4217.

(12) Sorg, A.; Brückner, R. *Synlett* **2005**, 289.

(13) (a) For a review see: Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235 and references therein.

(14) Crystal data for **4**: $C_{15}H_{18}O_4$, M_r = 262.29, orthorhombic, space group $P2_12_12_1$, a = 6.3696(2) Å, b = 7.2069(2) Å, c = 29.103(1) Å, V = 1335.97(7) Å^3, Z = 4, ρ_{calcd} = 1.304 g cm^{-3}, Mo Kα radiation (λ = 0.71073 Å, μ = 0.094 mm^{-1}), T = 100 K, R = 0.0388 ($F^2 > 2\sigma$), R_w = 0.1003 (for 1969 data and 173 refined parameters). CCDC 602228 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.