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Approach to the Tricyclic Core of the Tigliane−Daphnane Diterpenes. Concerning the Utility of Transannular Aldol Additions

Arthur J. Catino, Alexandra Sherlock, Peyton Shieh, Joseph S. Wzorek, and David A. Evans*

*Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street,
Cambridge, Massachusetts 02138, United States*

evans@chemistry.harvard.edu

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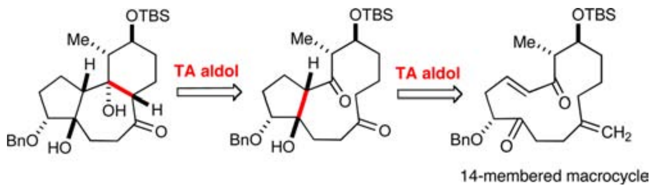
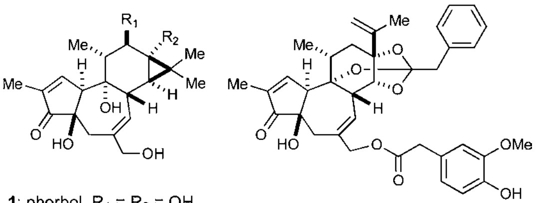
ABSTRACT



Two transannular (TA) aldol reactions were used to assemble the tricyclic carbon skeleton found in the tigliane and daphnane classes of diterpene natural products.

Polycyclic diterpenes have long provided the impetus for the development of new ring constructions.[1] Toward this end, the tricyclic ring system contained within the tigliane and daphnane families of diterpenes has received considerable attention (Figure 1).[2] Phorbol (**1**), for example, is a well-known tumor promotor and protein kinase C agonist.[3] Prostratin (**2**), 12-deoxyphorbol, is a promising theraputic agent that targets latent HIV reservoirs.[4] Resiniferatoxin (**3**) exhibits activity in common with capsaicin and is of interest as an analgesic agent.[5] The structural and biological attributes exhibited by these structures have identified them as enduring targets for chemical synthesis.[6]



1: phorbol, $R_1 = R_2 = OH$
2: prostratin, $R_1 = H$, $R_2 = OAc$

3: resiniferatoxin

Figure 1. Representative tigliane and daphnane diterpenes.

With an effort directed toward the synthesis of complex polycyclic motifs using transannular (TA) bond constructions,[7] we became aware that a macrocyclic approach to a

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(1) Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396.

(2) For synthetic approaches to the 5−7−6 ring system, see: Kogen, H. *J. Syn. Org. Chem. Jpn.* **1990**, *48*, 724.

(3) Newton, A. C. *Chem. Rev.* **2001**, *101*, 2353.

(4) (a) Johnson, H. E.; Banack, S. A.; Cox, P. A. *J. Nat. Prod.* **2008**, *71*, 2041. (b) Wender, P. A.; Kee, J.-M.; Warrington, J. M. *Science* **2008**, *320*, 649. (c) AIDS Research Alliance: About Prostratin. http://aidsresearch.org/cure-research/prostratin (accessed May 2013).

(5) (a) Szallasi, A.; Blumberg, P. M. *Neuroscience* **1989**, *30*, 515. (b) Blumberg, P. M.; Szallasi, A.; Acs, G. In *Capsaicin in the Study of Pain*; Wood, J. N., Ed.; Academic Press: London, 1993; p 45.

(6) For the total synthesis of each, see the following references. Phorbol: (a) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957. (c) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956. (d) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590. Prostratin: See ref 2.Resiniferatoxin: Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.

(7) (a) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (c) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968. (d) Wzorek, J. S.; Knöpfel, T. F.; Sapountzis, I.; Evans, D. A. *Org. Lett.* **2012**, *14*, 5841.

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5–7–6-ring system has not been forthcoming. Transannular reactions have long been implicated in the biosynthesis of these molecules from casbene, a 14-membered macrocycle (Figure 2).[8] Herein, we report a macrocyclic approach to the tricyclic core contained within the tigliane–daphnane ring system that employs two consecutive TA aldol reactions.

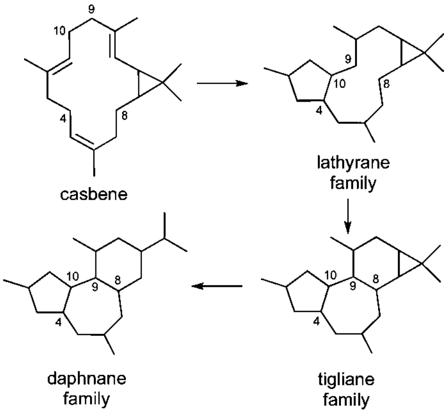
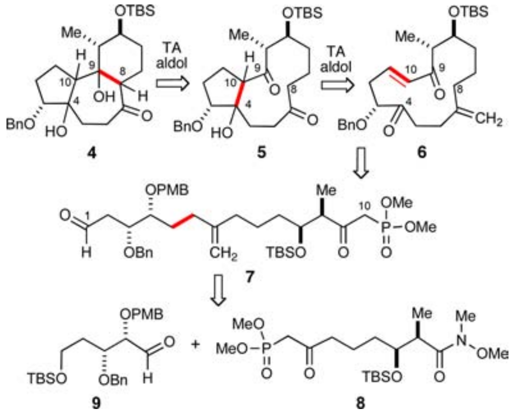


Figure 2. Unspecified transannular reactions implicated in the biosynthesis of tigliane and daphnane diterpenes.[8]

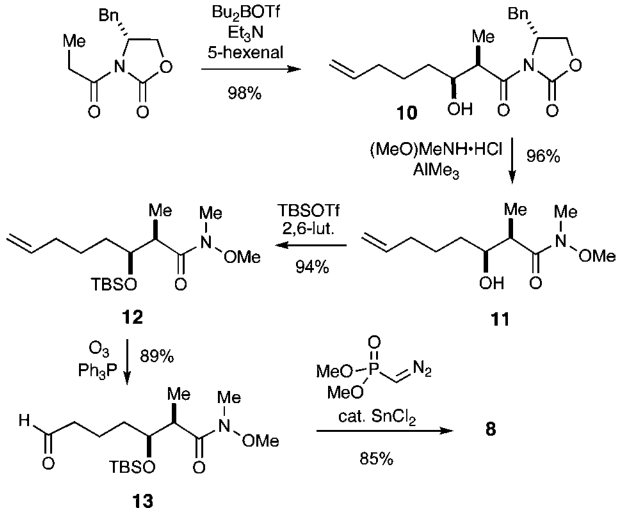
In our initial foray into the construction of the tigliane–daphnane ring system, we selected **4** as a target structure wherein the two internal bonds of the tricycle could be obtained through aldol constructions (Scheme 1). Considering that the stereochemical outcome of these reactions might be governed by the conformational preferences of the macrocycle,[9] we reasoned that a thermodynamically controlled TA aldol reaction could be used to form the C8–C9 bond (**5**→**4**); however, a kinetically controlled TA aldol reaction would be required to form the C4–C10 bond (**6**→**5**).[10] Regioselective enolate formation in the latter could be accomplished by hydride reduction of an enone.[11] An intramolecular Horner-Wadsworth-Emmons (HWE) reaction could be used to assemble macrocycle **6**, while an intermolecular HWE reaction could be employed to prepare linear precursor **7**. Enantiopure fragments **8** and **9** could then be prepared by conventional means.

The synthesis of fragment **8** began with an aldol addition of the enolborane derived from (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone with 5-hexenal to give *syn*-aldol adduct **10** in 98% yield (Scheme 2).[12] Trans-amination followed by protection of the secondary hydroxyl group gave **12** in high yield. Aldehyde **13** was obtained by ozonolysis of the terminal olefin. Finally, addition dimethyl diazomethylphosphonate[13] to aldehyde **13** (SnCl$_2$ catalysis) according to Roskamp's procedure[14] afforded β-ketophosphonate **8** in 85% yield.

Scheme 1. Synthesis Plan to the 5–7–6 Core



Scheme 2. Synthesis of Fragment **8**



The synthesis of fragment **9** is outlined in Scheme 3. Acetal **14** was obtained as a crystalline solid in three steps in 62% overall yield from tri-*O*-acetyl-D-glucal. Protection of the secondary hydroxyl group with benzyl bromide gave benzyl ether **15** in 94% yield. Regioselective acetal cleavage was accomplished using diisobutylaluminum hydride (DIBAL). The resultant primary alcohol was converted to iodide **16** with Ph$_3$P/I$_2$ in 88% over two steps. Metal–halogen exchange and subsequent ring-opening, followed by quenching with *tert*-butyldimethylsilyl triflate (TBSOTf) gave olefin **17** in 87%. Finally, ozonolysis delivered fragment **9**.

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(8) Adolf, W.; Hecker, E. *Isr. J. Chem.* **1977**, *16*, 75.

(9) For a review of macrocyclic stereocontrol, see: Carreira, E. M.; Kvaerno, L. Macrocyclic Stereocontrol. In *Classics in Stereoselective Synthesis*; Wiley-VCH: Verlag, 2009; p 1.

(10) 14-Membered rings are virtually free of ring strain. An aldol reaction to form a 5,11-ring system (∼16 kcal/mol of ring strain) under thermodynamic conditions would invariably favor the 14-membered ring.

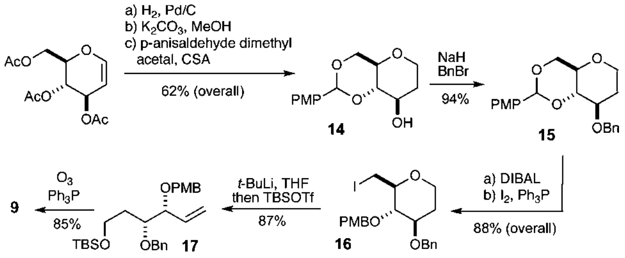
(11) For a review of enones as latent enolates, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12.

(12) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

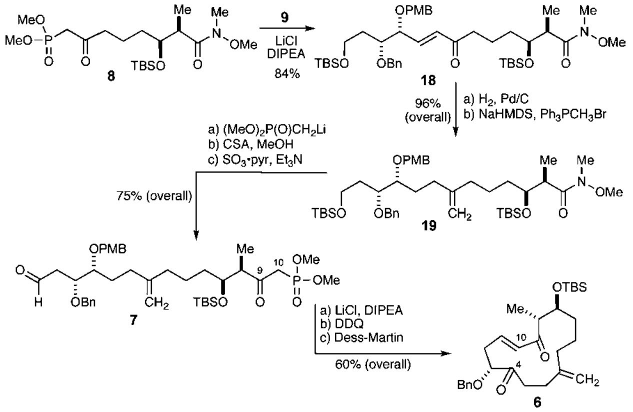
(13) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.

(14) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

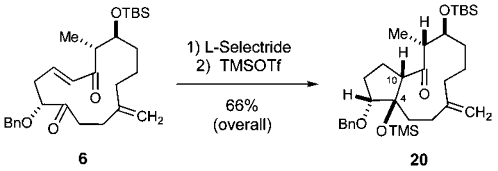
Scheme 3. Synthesis of Fragment **9**



Scheme 4. Fragment Coupling and Macrocyclization



Scheme 5. C4–C10 Transannular Aldol Reaction



Fragments **8** and **9** were coupled using an HWE reaction under Masamune–Roush conditions[15] to give enone **18** in 84% yield (Scheme 4). Hydrogenation and Wittig methylenation afforded **19** in 96% yield. Formation of the β-ketophosphonate, selective removal of the primary TBS group, and oxidation of the resultant alcohol gave aldehyde **7**. An intramolecular HWE reaction afforded the desired macrocycle (> 95:5 *E*/*Z* selectivity) and its dimer as a 3:1 inseparable mixture in 98% yield. Subsequent treatment with DDQ to remove the PMB group followed by oxidation of the secondary alcohol with Dess–Martin periodinane provided macrocyclic ketone **6** in 60% yield over three steps.[16]

Treatment of macrocyclic ketone **6** with L-Selectride in THF at −78 °C afforded an aldol product that was immediately silylated with TMSOTf to provide **20** as a single diasteriomer in 66% yield over two steps (Scheme 5).[17,18] The cis ring fusion was readily deduced by NOESY correlations. Silyl protection of the tertiary alcohol was mandatory due to facile retroaldolization driven by the release of strain in the 11-membered ring.[10] Indeed, the 14-membered diketone (not shown) was observed as a side product in the reaction which we suspect arises from retro-aldolization and subsequent protonation of the enolate.

The observed diastereoselectivity in the C4–C10 TA aldol reaction may be attributed to the formation of a stereochemically well-defined lithium enolate[19] that undergoes reaction via an open transition state. Chamberlin and Reich have shown that enolate geometry (*E* or *Z*) in conjugate reductions with L-Selectride is dictated by the ground-state conformational preference of the enone under non-Curtin–Hammett constraints.[20] Accordingly, a Monte Carlo conformational search using MMFF[21] identified *s-cis*-**21** as the lowest energy enone conformer (Figure 3). Considering the difference in energy (> 3.0 kcal/mol) between *s-cis* and *s-trans* enones, selective formation of the (*Z*) lithium enolate may be anticipated. Relative energies of the diastereomeric transition states were approximated by constraining the distance between the enolate and carbonyl carbons and undertaking a second conformational search.[22] The conformation in which the enolate and carbonyl oxygens are oriented on opposite sides of the macrocyclic plane leading to an open transition state (**TS1**) was found to be the lowest in energy. The conformation leading to an apparent closed transition state (**TS2**) was calculated to be 5.3 kcal/mol higher in energy. On the basis of this difference in energy and considering that the trialkylborane generated in situ can activate the carbonyl group, an open transition is likely. Intermoleclar reductive aldol reactions mediated by L-Selectride reported by Ghosh[23] are also believed to proceed via an open transition state and lend support to this conclusion.

With bicyclic intermediate **20** in hand (Scheme 5), the second TA aldol reaction to form the C8–C9 bond was

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(15) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(16) The 28-membered ring dimer was readily separated from the desired macrocycle by flash chromatography after the Dess–Martin oxidation. See the Supporting Information for full characterization.

(17) For conjugate reduction with L-Selectride as a means of enolate formation, see: Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

(18) Stryker's reagent ($[(PPh_3)CuH]_6$) was also effective as a hydride source. For reductive aldol reactions with Stryker's reagent, see: Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901.

(19) Conjugate reduction with L-Selectride favors the formation of a lithium enolate as opposed to a boron enolate. The yield of boron enolate, however, has been shown to be highly dependent on the alkali-metal cation in the order of K > Na > Li; see: Ma, L.; Hopson, R.; Li, D.; Zhang, Y.; Williard, P. G. *Organometallics* **2007**, *26*, 5834.

(20) Chamberlin, A. R.; Reich, S. H. J. *Am. Chem. Soc.* **1985**, *107*, 1440.

(21) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

(22) A transition-state distance constraint of 2.1 Å was employed in this computation; see: Lewars, E. G. *Computational Chemistry: Introduction to the Theory and Applications of Molecular and Quantum Mechanics*, 2nd ed.; Springer: Dordrecht, 2011; p 63.

(23) Ghosh, A. K.; Kass, J.; Anderson, D. D.; Xu, X.; Marian, C. *Org. Lett.* **2008**, *10*, 4811.

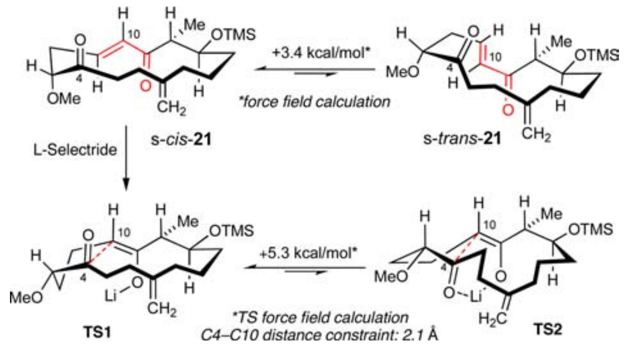
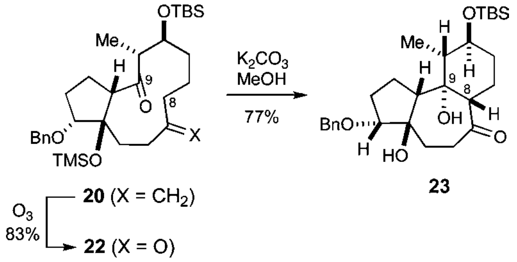


Figure 3. Rationale for the observed selectivity in the C4–C10 TA aldol reaction (three-dimensional structures have been rendered in ChemDraw for clarity).

undertaken (Scheme 6). Ozonolysis afforded diketone **22** (83%) which was then treated with base (K_2CO_3/MeOH)[24] to induce a TA aldol reaction to give tricycle **23** in 77% yield as a single diatereromer having a trans-ring fusion. In the course of the reaction, the C4 hydroxyl group undergoes desilylation *after* the C8–C9 TA aldol reaction as judged by ^{1}H NMR and TLC analysis. The stereochemical outcome of this TA aldol reaction is attributed to the formation of the thermodynamically most stable trans-ring fused product (vide infra). The corresponding cis-fused product was found to be 3.3 kcal/mol higher in energy.[25]

Scheme 6. C8–C9 Transannular Aldol Reaction



In summary, we report a macrocyclic approach to the tricyclic core of the tigliane and daphnane classes of diterpene natural products. Two transannular aldol reactions enabled the construction of the tricyclic ring system. This study demonstrates the value of aldol constructions for complex polycyclic synthesis and the unique suitibility of macrocycles to control the stereochemical outcome. Further studies of these reactions are anticipated.

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Supporting Information Available. Experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[24] Shizuri, Y.; Ohtsuka, J.; Kosemura, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 5547.

[25] Semiempirical PM3 caculations were performed on Spartan08.

The authors declare no competing financial interest.