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Stereocontrolled Construction of Either Stereoisomer of 12-Oxatricyclo[6.3.1.0^{2,7}]dodecanes Using Prins–Pinacol Reactions

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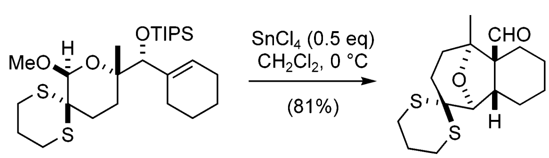
ABSTRACT



12-Oxatricyclo[6.3.1.0^{2,7}]dodecanes can be efficiently synthesized in a stereoselective manner by Prins–pinacol reactions. By biasing the transition state of the Prins cyclization, it is possible to access either stereoisomer of this oxatricyclic ring system.

The Prins−pinacol reaction is a powerful method to construct complex carbo- and oxacyclic ring systems. Various natural products containing fused or bridged rings have been synthesized using this reaction as the central strategic step.[1] In the context of ongoing efforts to synthesize the fungal metabolite aspergillin PZ (**1**), we report herein that the Prins−pinacol reaction can be tuned to construct either stereoisomer of the 12-oxatricyclo[6.3.1.0^{2,7}]dodecane ring system.

Aspergillin PZ (**1**) is an isoindolone alkaloid isolated recently by Pei and co-workers from the soil fungus *Aspergillus awamori*.[2] It is an attractive target for total synthesis because of its antitumor activity and the challenge involved in constructing its unique pentacyclic ring system, which features eight contiguous stereocenters and a 12-oxatricyclo[6.3.1.0^{2,7}]dodecane moiety. A related oxatricycloundecane unit is found in several members of the salvialane sesquiterpene family, exemplified by 1,5-epoxysalvial-4(14)-ene (**2**) (Figure 1).[3] The relative configuration of the three rings in the natural products **1** and **2** differs: in aspergillin PZ (**1**) the fused and bridged rings are oriented in a trans fashion about the central tetrahydrofuran ring, whereas in 1,5-epoxysalvial-4(14)-ene (**2**) they are displayed cis (Figure 2).

Our plan for preparing aspergillin PZ (**1**) is based upon two strategic disconnections: an intramolecular Diels−Alder cyclization (**5** → **1**) to form the isoindolone unit[4] and a Prins−pinacol reaction (**7** → **6**) to construct the 12-oxatricyclo[6.3.1.0^{2,7}]dodecane core (Scheme 1).

In the proposed Prins−pinacol reaction, formation of the correct relative configuration of the 12-oxatricyclo[6.3.1.0^{2,7}]-

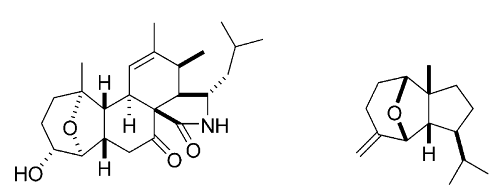


Figure 1. Natural products containing bridged oxatricyclic ring systems.

(1) For a recent review, see: Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.
(2) Zhang, Y.; Wang, T.; Pei, Y.; Hua, H.; Feng, B. *J. Antibiot.* **2002**, *55*, 693−695.
(3) Maurer, B.; Hauser, A. *Helv. Chim. Acta* **1983**, *66*, 2223−2235.

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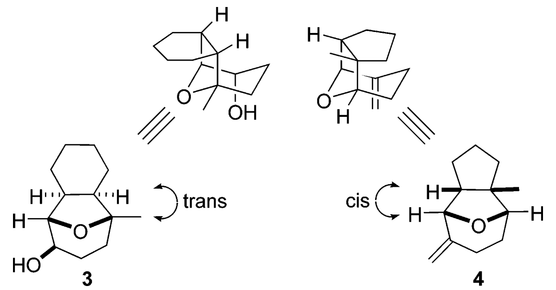
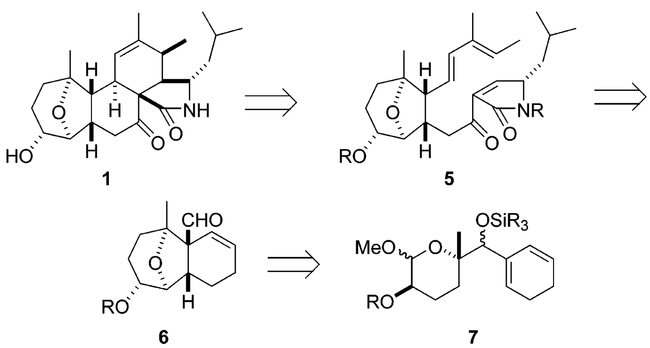


Figure 2. Comparison of the oxatricyclic ring systems **3** and **4** contained in aspergillin PZ (**1**) and 1,5-epoxysalvial-4(14)-ene (**2**).

dodecane moiety requires that the Prins cyclization takes place by a boat topography (Scheme 2). Cyclization occurring through a chair topography would afford an 12-oxatricyclo-[6.3.1.0^{2,7}]dodecane having the configuration found in the congeneric unit of 1,5-epoxysalvial-4(14)-ene (**2**). In general, Prins cyclizations that form six-membered rings occur by chair topographies,[5] which has been the case in previous Prins−pinacol reactions reported from our laboratories.[1] In the reaction pathways analyzed in Scheme 2, we conjectured that the chair process might be disfavored because of the cofacial disposition of the two six-membered rings in the conversion **8** → **9** (Scheme 2).

Scheme 1. Retrosynthetic Analysis of Aspergillin PZ (**1**)



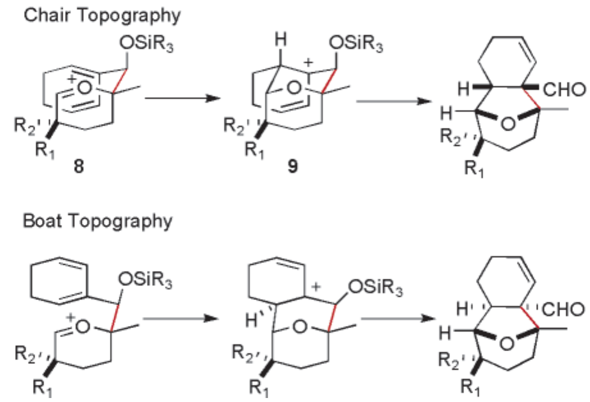
As there was no precedent for the projected Prins−pinacol reaction **7** → **6**, we set out to explore the feasibility of this transformation in simpler systems. Synthesis of the first model substrate was accomplished by halogen−lithium exchange of 1-iodocyclohexene[6] (**11**) with *t*-BuLi, followed

(4) This strategy has been employed widely in the synthesis of alkaloids containing the isoindolone unit such as cytochalasin D and aspochalasin C; see: (a) Harkin, S. A.; Jones, R. H.; Tapolczay, D. J.; Thomas, E. J. *Chem. Soc., Perkin. Trans. 1* **1989**, 489−497. (b) Craven, A. P.; Dyke, H. J.; Thomas, E. J. *Tetrahedron* **1989**, *45*, 2417−2429. (c) Thomas, E. J.; Watts, J. P. *Chem. Soc., Perkin. Trans. 1* **1999**, 3285−3290.

(5) For reviews of Prins cyclizations, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *52*, 505−555. (b) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions;* Trost, B. M., Fleming, I., Heathcock, C. H., Ed.; Pergamom Press: New York, 1991; Vol. 2, pp 527−561.

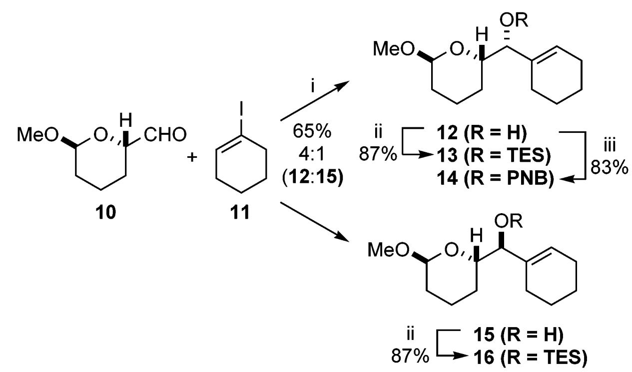
(6) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147−162.

Scheme 2. Stereoselection in Prins−Pinacol Reactions Assembling 12-Oxatricyclo[6.3.1.0^{2,7}]dodecanes



by the addition of hydropyran aldehyde **10** (Scheme 3).[7] The resulting 4:1 mixture of alcohols **12** and **15** was separated by HPLC, and the resulting pure epimers were silylated to provide Prins−pinacol precursors **13** and **16**. The relative configuration of these epimers was confirmed by single-crystal X-ray analysis of the *p*-nitrobenzoyl ester derivative **14** of alcohol **12**.[9]

Scheme 3. Synthesis of Prins−Pinacol Precursors **13** and **16**[a]



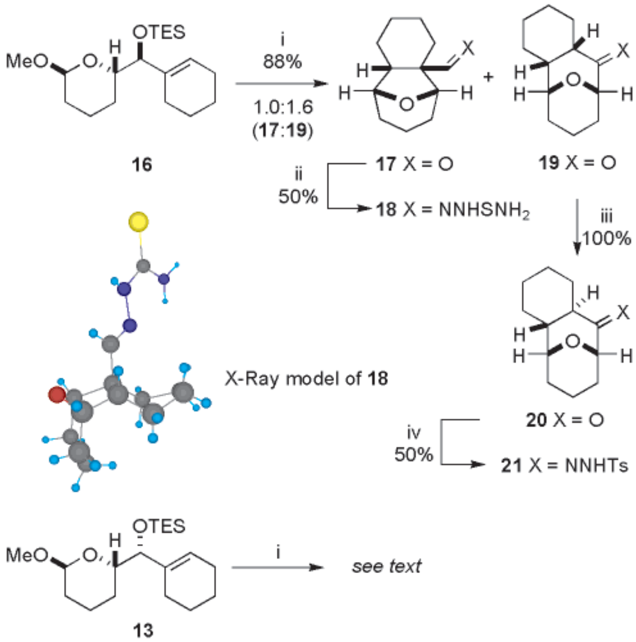
[a] Reagents and conditions: (i) *t*-BuLi, then **11**, THF, −78 °C; (ii) TESCl, imidazole, DMF, rt; (iii) 4-nitrobenzoyl chloride, pyr, DMAP, CH_2Cl_2.

Cyclohexenyl acetals **13** and **16** were exposed to several Lewis acids in order to initiate their Prins−pinacol conversions. Transformations of acetal **16** were found to be cleanest in the presence of $SnCl_4$. For example, reaction of **16** with 0.5 equiv of $SnCl_4$ in CH_2Cl_2 for 0.5 h at 0 °C provided a mixture of the 12-oxatricyclo[6.3.1.0^{2,7}]dodecane aldehyde **17** (33%) and 13-oxatricyclo[7.3.1.0^{0,0}]tridecan-8-one **19** (55%) (Scheme 4).[8] In contrast, exposure of **13** to identical reaction conditions afforded a complex mixture of products

(7) Jurczak, J.; Bauer, T.; *Tetrahedron* **1986**, *42*, 5045−5052.

(8) Prins-pinacol reaction of the TIPS analogue of **16** under similar conditions provided oxatricyclic products **17** and **19** in a 3:1 ratio (^{1}H NMR analysis).

Scheme 4. Prins-Pinacol Cyclization of Model Systems **13** and **16**[a]



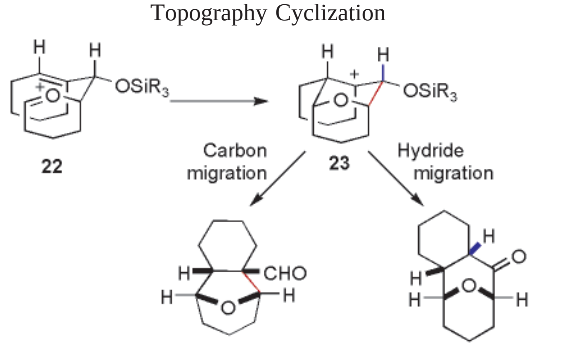
[a] Reagents and conditions: (i) $SnCl_4$, CH_2Cl_2, 0 °C; (ii) thiosemicarbazide, AcOH; (iii) DBU, benzene, 60 °C; (iv) tosyl hydrazine, AcOH.

in which aldehyde **17** and a second aldehyde of unknown structure were present in equal amounts (^{1}H NMR analysis), albeit in low yield.

Structures of the tricyclic products formed from cyclohexenyl acetal **16** were established as follows. The constitution and relative configuration of **17** was confirmed by single-crystal X-ray analysis of thiosemicarbazone derivative **18**.[9] Ketone **19** was equilibrated to the thermodynamically more stable epimer **20**, which provided a tosylhydrazone derivative **21** suitable for single-crystal X-ray analysis.[9]

Formation of the *cis*-12-oxatricyclo[6.3.1.0^{2,7}]dodecane aldehyde **17** from Prins−pinacol transformation of **16** establishes that cofacial orientation of the two six-membered rings is feasible with Prins cyclization occurring by a chair topography (**22** → **23**). The byproduct, oxatricyclotridecanone **19**, would arise from the resulting carbenium ion intermediate **23** undergoing hydride migration competitively with migration of the ring bond (Scheme 5).

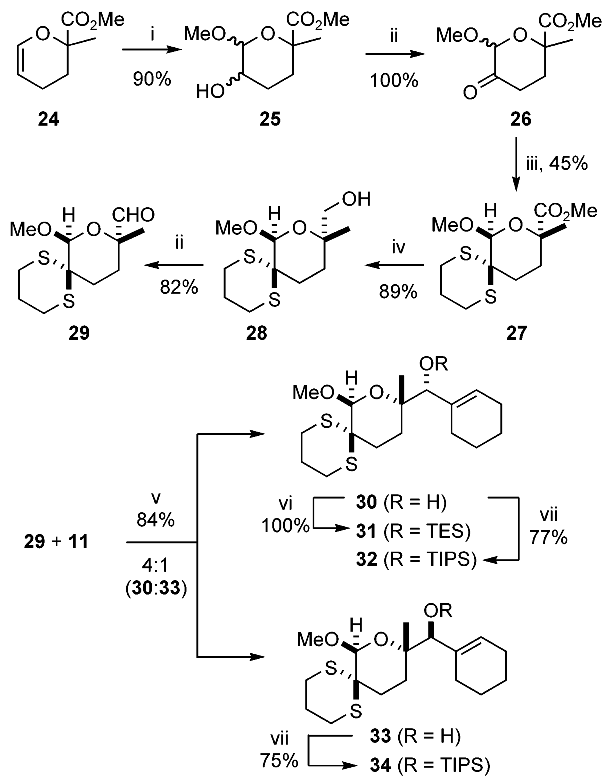
Scheme 5. Hydride versus Carbon Bond Migration in a Chair Topography Cyclization



To favor a boat topography for the Prins cyclization, we chose to introduce additional steric hindrance between the cofacial six-membered rings by having the R^2 substituent of the generalized sequence depicted in Scheme 2 be a group other than hydrogen. In the context of a synthetic approach to aspergillin PZ (**1**), incorporating a 1,3-dithiane as a carbonyl surrogate adjacent to the oxocarbenium ion was particularly appealing.

The synthesis of such a Prins−pinacol precursor is outlined in Scheme 6. The sequence commenced with the reaction of dihydropyran **24**[10] with *m*-CPBA in MeOH to deliver tetrahydropyran **25**, which upon Swern oxidation provided ketone **26** as a mixture of methoxy anomers.[11] Subsequent treatment of this keto acetal with propanedithiol and BF_3·

Scheme 6. Synthesis of Prins−Pinacol Precursors in the Dithiane Series[a]



[a] Reagents and conditions: (i) *m*-CPBA, MeOH, 0 °C; (ii) oxalyl chloride, DMSO, Et_3N; (iii) propanedithiol, BF_3·OEt_2, CH_2Cl_2, rt; (iv) $LiAlH_4$, Et_2O; (v) *t*-BuLi, then **11**, Et_2O, −78 °C; (vi) TESCl, imid, DMF; (vii) TIPSOTf, pyr, DMAP, CH_2Cl_2, rt.

(9) Crystallographic data for this compound was deposited at the Cambridge Crystallographic Data Centre; CCDC numbers: **14**, 249137; **18**, 249133; **21**, 249132; **29**, 249135; **31**, 249134; **37**, 249136.

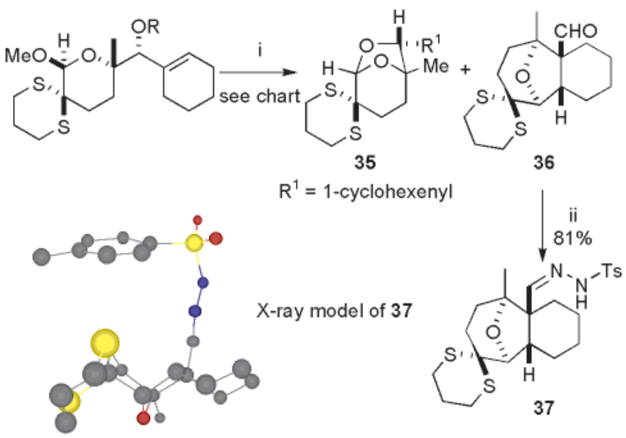
(10) Smith, C. W.; Norton, D. G.; Ballard, S. A. *J. Am. Chem. Soc.* **1951**, *73*, 5270−5272.

(11) Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

OEt_2 yielded the desired 1,3-dithiane **27** as a 4:1 mixture of methoxy anomers. The major anomer, isolated by flash chromatography in 45% yield, was advanced through a standard reduction/oxidation sequence to produce aldehyde **29**. At this point, the relative configuration of the two stereocenters of **29** could be established by single-crystal X-ray analysis.[9] Coupling of aldehyde **29** with cyclohexenyllithium provided a 4:1 mixture of alcohol epimers **30** and **33**. These diastereomers were separated by HPLC and independently silylated to generate potential Prins-pinacol substrates **31**, **32,** and **34** (Scheme 6). The triethylsilyl derivative **31** provided single crystals, allowing its relative configuration to be established by X-ray analysis.[9]

Prins−pinacol rearrangement in the dithiane series was investigated initially with triethylsilyl derivative **31**. Exposing this intermediate to $SnCl_4$ (0.5 equiv) for 0.5 h at 0 °C in CH_2Cl_2 provided a 3:1 mixture of the tricyclic acetal **35** and the desired *trans*-12-oxatricyclo[6.3.1.0^{2,7}]dodecane aldehyde **36** (Scheme 7). The relative configuration of this latter product was signaled initially by the <1 Hz coupling constant observed between its angular hydrogen and the adjacent hydrogen of the tetrahydrofuran ring. This coupling would only be expected if the dihedral angle between these hydrogens is ∼90°.[12] The relative configuration of **36** was confirmed subsequently by single-crystal X-ray analysis of tosylhydrazone derivative **37**.[9]

Scheme 7. Prins−Pinacol Cyclizations[a]



entry	R	ratio (**35**:**36**)[b]	yield
1 (**30**)	H	(>20:1.0)	99%
2 (**31**)	TES	(3.0:1.0)	nd
3 (**32**)	TIPS	(1.0:>20)	81%

[b] as determined by ^{1}H NMR

[a] Reagents and conditions: (i) $SnCl_4$ (0.5 eq), CH_2Cl_2, 0 °C; (ii) $TsNHNH_2$, AcOH.

The competitive formation of tricyclic acetal **35** most likely results from partial loss of the $SiEt_3$ group under the reaction conditions. Supporting this theory, $SnCl_4$-promoted reaction of hydroxy acetal **30** under identical reaction conditions yielded cyclic acetal **35** as the sole product. Buffering the reaction of triethylsilyl acetal **31** with 0.5 equiv of 4-methyl-2,6-di-*tert*-butylpyridine did not fully inhibit formation of cyclic acetal **35**.[13] Accordingly, the more robust TIPS silyl ether **32** was examined. In this case, Prins−pinacol reaction occurred cleanly to provide *trans*-oxatricyclododecane aldehyde **36** in 81% isolated yield (Scheme 7). As observed in the earlier model series, the stereoisomeric triisopropylsiloxy acetal **34** afforded an intractable mixture of products under identical reaction conditions.

In summary, using a Prins−pinacol strategy, it is possible to stereoselectively construct 12-oxatricyclo[6.3.1.0^{2,7}]dodecanes having either the cis or trans relationship of the fused and bridged rings that adorn the central tetrahydrofuran unit. With sterically unbiased substrates, the Prins cyclization preferentially occurs in a chair topography to yield the cis stereoisomer. However, it is also possible to exploit unfavorable steric interactions to disfavor the chair transition structure and force the reaction to proceed through a boat topography to provide the stereoisomeric trans oxatricyclic product. This latter result lends credence to the synthetic approach to aspergillin PZ (**1**) adumbrated in Figure 1.

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Supporting Information Available: Experimental procedures for the preparation of **12**−**21** and **27**−**37**; tabulated characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A coupling of 4.2 Hz is observed between the corresponding hydrogens of **17**.

(13) The ratio of **35**/**36** in this case was 1:1.