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Stereoselective Synthesis of the Octahydronaphthalene Unit of Integramycin via an Intramolecular Diels–Alder Reaction

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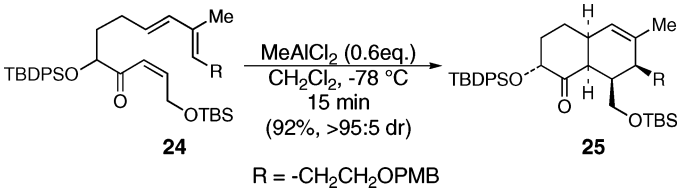
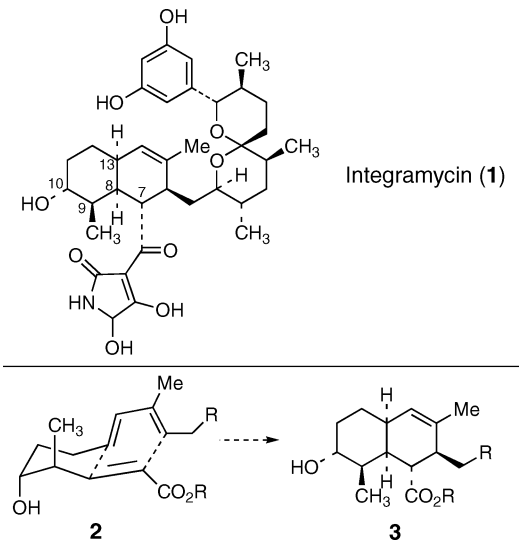
ABSTRACT



The racemic *cis*-decalin core fragment 30 of integramycin was synthesized by a sequence involving a highly diastereoselective intramolecular Diels–Alder reaction of triene 24. A remarkable switch in stereoselectivity occurred upon changing the dienophile unit of 24 from (*Z*)- to (*E*)-geometry.

Integramycin (**1**, Scheme 1), a structurally novel HIV-1 integrase inhibitor (IC_{50} = 4 μM), was isolated from *Actinoplanes* extracts by Singh and co-workers in 2002.[1] Integramycin contains a central *cis*-octahydronaphthalene unit with acyl tetramic acid and spiroketal-containing side chains. Thus far, the only synthetic effort directed toward integramycin was published by Floreancig, who reported a synthesis of the spiroketal fragment.[2]

Scheme 1. Integramycin and Proposed Biogenesis of the *cis*-Decalin Core via an IMDA Reaction



It has been suggested[3] that the biosynthesis of the *cis*-octahydronaphthalene core unit of integramycin might arise via an *exo*-selective intramolecular Diels−Alder reaction (IMDA)[3,4] of an appropriate triene, as in **2**. However, our analysis of this hypothesis indicated that such a transition state (**2**) should be disfavored because of the axial orientation of the hydroxyl and methyl substituents in the chairlike conformation of the connecting chain. Therefore, a synthetic approach relying on an IMDA reaction to form the octahydronaphthalene core fragment would have to include appropriate strategies for stereochemical control of this reaction. We report herein a highly stereoselective synthesis of the

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(2) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569.
(3) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321.
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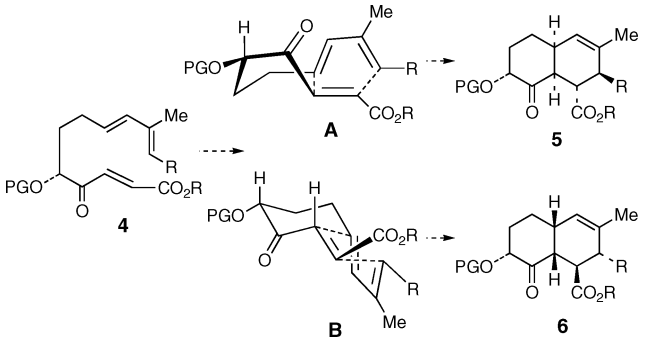
cis-fused octahydronaphthalene core unit of integramycin via an IMDA reaction of trienone **24**. We also present our observations of the dependence of the cis vs trans selectivity of IMDA reactions of 1,7,9-decatrien-3-ones on the stereochemistry of the dienophilic double bond.

Our synthetic strategy is predicated on the expectation that cis-fused octahydronaphthalenone **5** (Scheme 2) should be

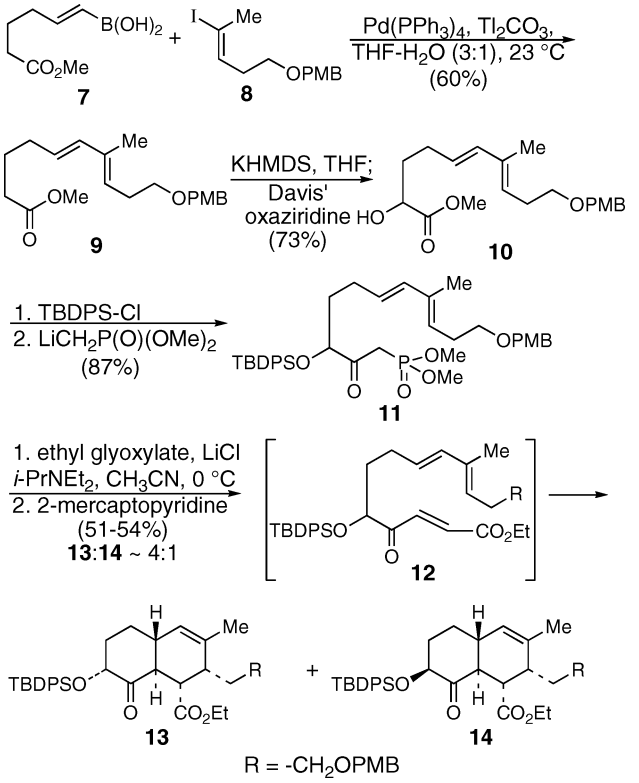
Scheme 2. IMDA Transition State Analysis



a viable precursor to the targeted integramycin ring system, **3**. Further, we anticipated that intermediate **5** could be accessed by the IMDA reaction of trienone **4** (Scheme 2). Previous studies in this laboratory have implicated the intervention of boatlike transition states in the IMDA reactions of 1,7,9-decatrien-3-ones.[5] Moreover, those studies indicated that in the absence of overriding nonbonded interactions, boatlike transition states should predominate in the IMDA reactions of these substrates.[4,5] We reasoned, therefore, that the IMDA reaction of a trieneone **4**, containing the protected C(10)−OH group of integramycin, would proceed through boatlike transition state **A** to give *cis*-decalin **5** (Scheme 2). The alternative chairlike transition state **B** would lead to *cis*-decalin **6**, with the incorrect stereochemistry for integramycin.

We elected to synthesize racemic triene **12** to test this hypothesis (Scheme 3). This synthesis began with the thallium carbonate[6] promoted Suzuki coupling[7] of known vinylboronic acid **7**[8] and vinyl iodide **8**[9] to give diene **9** in 60% yield. Treatment of **9** with KHMDS in THF at −78 °C followed by addition of Davis' oxaziridine (*trans*-2-(phenylsulfonyl)-3-phenyloxzairidine)[10,11] provided the α-hydroxy methyl ester **10** in 73% yield. Treatment of the derived TBDPS ether with dimethyl lithiomethylphosphonate gave *β*-keto phosphonate **11** in 87% yield over two steps. Subjection of **11** to a Horner−Wadsworth−Emmons olefi-

Scheme 3. Synthesis and IMDA Reaction of Triene **12**



nation[12] with ethyl glyoxylate, followed by addition of 2-mercaptopyridine to isomerize any (*Z*)-olefin formed,[5] resulted in the generation and in situ cyclization of **12** to an inseparable ca. 4:1 mixture of trans-fused bicycles **13** and **14**. The isomeric cycloadducts were separated after deprotection of the PMB ethers. The stereochemistry of the two adducts was then assigned on the basis of NOE and coupling constant analysis (see Supporting Information).

The production of trans-fused cycloadducts **13** and **14** was unexpected given the literature precedent for IMDA reactions of similar substrates.[4] To probe the possibility that the dienophilic carboethoxy group might be responsible for the trans selectivity, we examined the IMDA reaction of **15** with a monoactivated dienophile.

Subjection of **11** to the HWE reaction[12] with α-benzyloxy acetaldehyde produced triene **15** in 82% yield (Scheme 4). Treatment of **15** with 1.5 equiv of $MeAlCl_2$ at −78 °C then provided trans-fused cycloadduct **16** in 72% yield, along with a small amount of another isomer that could not be purified or identified. The stereochemistry of **16** was assigned by ^1H NOE and coupling constant analysis after deprotection of the PMB ether (see Supporting Information).

At this point, we became concerned that the bulky C(10)-OTBDPS group might be responsible for the exclusive production of trans-fused products in the IMDA reaction. To determine the selectivity of an IMDA substrate lacking

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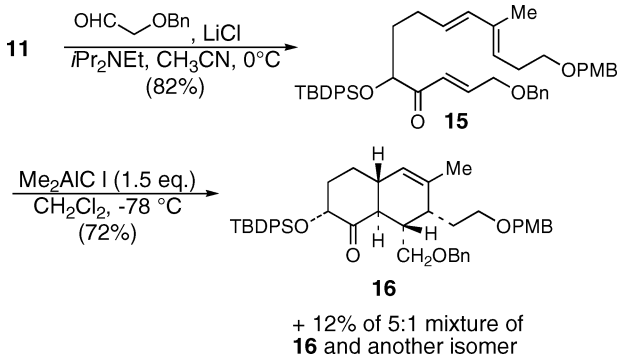
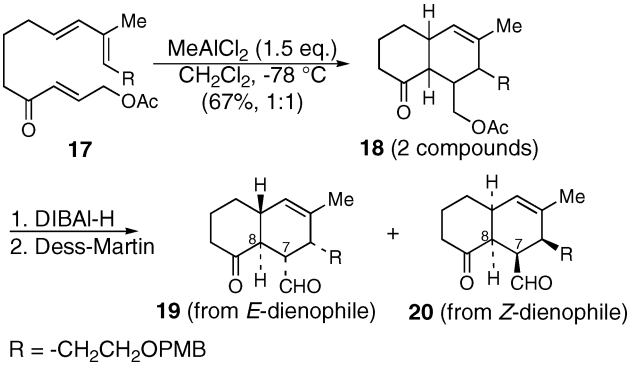
(12) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186.

Scheme 4. IMDA Reactions of Triene **15**



this group, we synthesized triene **17** (Scheme 5). Treatment of **17** with $MeAlCl_2$ in CH_2Cl_2 at −78 °C gave two cycloadducts in ca. 1:1 ratio. These products were identified by oxidation of the derived primary alcohols to give trans-

Scheme 5. IMDA Reactions of Triene **17**

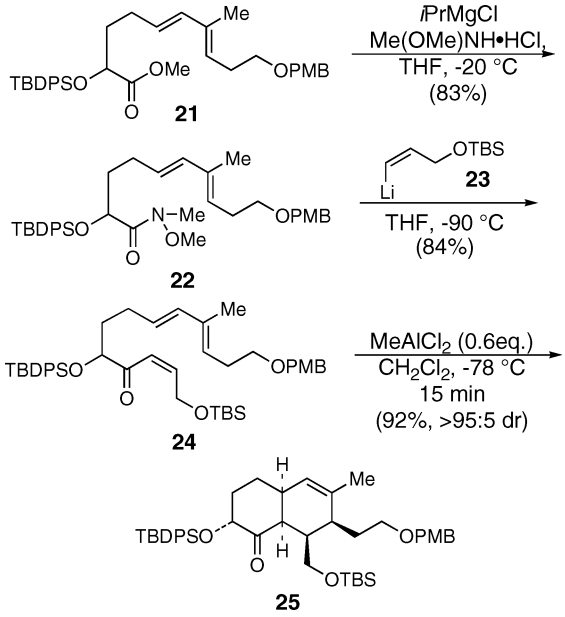


fused **19** and cis-fused **20**. The stereochemistry of **20** is surprising because the C(7) substituent is trans to the C(8)-H, a result that could arise either by epimerization of C(8) under the IMDA reaction or from the IMDA reaction of the (*Z*)-dienophile isomer of **17**. Given that it seemed unlikely that epimerization of C(8) occurred during the IMDA reaction, we thought it possible that triene **17** partially isomerized to a (*Z*)-dienophile in the presence of $MeAlCl_2$, and that the isomeric (Z)-triene underwent the IMDA reaction to provide the cis-fused cycloadduct **20**. If this analysis is correct, then the IMDA reaction of triene **24** containing a (*Z*)-dienophile would provide access to the targeted cis-fused intermediate **25** (Scheme 6).

Accordingly, methyl ester **21** was treated with Me(OMe)-NH·HCl and *i*PrMgCl[13] to give the Weinreb amide **22** in 83% yield. Addition of vinyllithium **23**[14] to **22** at −90 °C provided triene **24** in 84% yield. *To our delight, when* ***24*** *was treated with 0.6 equiv of* $MeAlCl_2$ *in* CH_2Cl_2 *at −78 °C for only 15 min, cis-fused decalin* ***25*** *was produced in 92%*

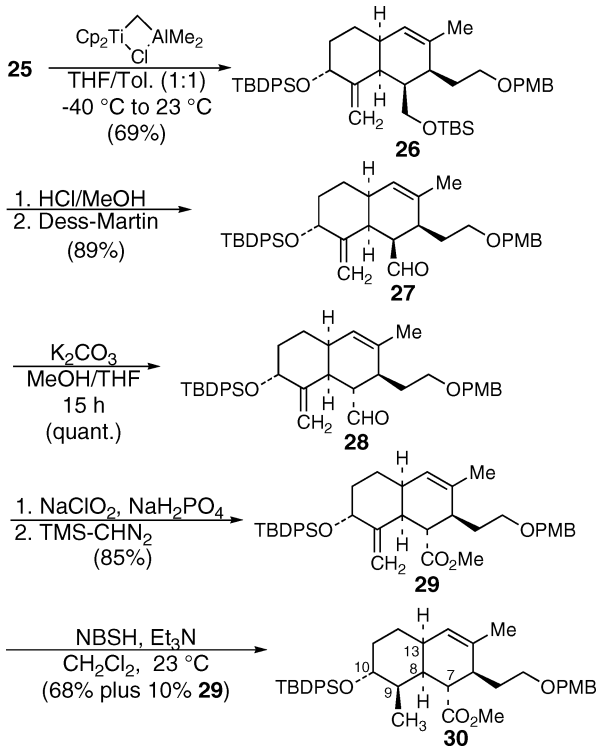
(13) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(14) Araki, Y.; Konoike, T. *J. Org. Chem.* **1997**, *62*, 5299.

Scheme 6. Synthesis and IMDA Reaction of Triene **24**



yield with >95:5 diastereoselectivity. The stereochemistry of **25** could not be determined directly, so it was treated with Tebbe reagent[15] to give the diene **26** in 69% yield (Scheme 7). Acidic deprotection of the primary TBS ether, followed by oxidation of the resulting alcohol with the Dess−Martin

Scheme 7. Elaboration of *cis*-Decalin **25** to the Octahydronaphthalene Nucleus of Integramycin[a]



[a] NBSH = *o*-nitrobenzenesulfonylhydrazide.

periodinane,[16] furnished aldehyde **27** in 89% yield. Aldehyde **27** was suitable for stereochemical analysis and identified as a cis-fused compound on the basis of $J_{8,13} = 6.6$ Hz and observation of ^{1}H NOE between the ring fusion protons H(8) and H(13). The stereochemistry of the critical C(10)-alkoxy substituent was confirmed by an NOE interaction between H(10) and the aldehyde C−H (see Supporting Information).

To complete the synthesis of the integramycin core structure, aldehyde **27** was treated with K_2CO_3 in THF−MeOH at 23 °C to provide the C(7) epimer **28** in quantitative yield. The aldehyde was then oxidized to the carboxylic acid, which after treatment with $TMSCHN_2$ gave methyl ester **29** in 85% yield. Finally, reduction of the *exo*-methylene with a large excess of diimide (generated in situ from *o*-nitrobenzenesulfonylhydrazide[17,18] and Et_3N) provided **30** in 68% yield; approximately 10% of starting material **29** was recovered. The C(9)-methyl stereochemistry was confirmed by coupling constant analysis ($J_{8,9} = 3.7$ Hz, $J_{9,10} = 10.3$ Hz), as were the cis ring fusion ($J_{8,13} = 3.7$ Hz) and C(7)−CO_2Me ($J_{7,8} = 10.7$ Hz) configurations. Structure **30** therefore contains all of the stereochemical elements of the cis-fused octahydronaphthalene core structure of integramycin.

Modest differences in the cis vs trans ring fusion selectivity of IMDA reactions of substituted 1,7,9-decatrien-3-ones containing (*E*)- and (*Z*)-dienophiles have been noted previously.[14] The complete reversal in ring fusion selectivity that we observed upon switching from an (*E*)-dienophile (as in **15**, which provides trans-fused **16** exclusively) to a (*Z*)-dienophile (as in **24**, which provides cis-fused **25** with 20:1 selectivity), however, is quite remarkable. IMDA reactions of 1,7,9-decatrien-3-ones are believed to proceed via a concerted but nonsynchronous transition state in which bonding at the C(1)−C(10) carbons (triene numbering) is more advanced than at C(4)−C(9).[4] This leads to a "skewing" (or twisting) of the plane of the dienophile relative to the diene in order to minimize steric repulsion between these two units in the transition state.[4,19] In the IMDA reaction with an (*E*)-dienophile, transition state **31** (Figure 1) leading

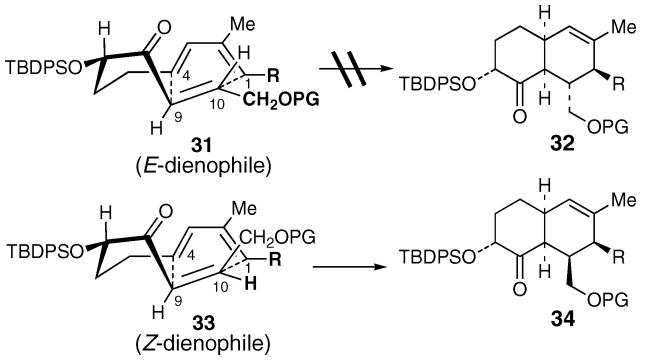


Figure 1. Cis/Trans Selectivity in the IMDA Reaction.

to the cis-fused product **32** is disfavored because of a near-eclipsing steric interaction between the −CH_2OPG unit and the R group of the diene. This interaction is less severe in transition state **33**, in which case the C(1)−C(10) developing bond is nearly staggered, and as a result, **24** the (*Z*)-dienophile substrate leads to the cis-fused product **34**.

In summary, we have achieved an efficient synthesis of the racemic *cis*-octahydronaphthalene unit **30** of integramycin via a diastereoselective IMDA reaction of triene **24**. We have also described a remarkable switch in cis vs trans ring fusion selectivity for trienes with an (*E*)- or (*Z*)-dienophile geometry. Further studies toward the total synthesis of integramycin will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H NMR, ^{13}C NMR, IR, HRMS) for all new compounds and stereochemical determinations for compounds **19**, **20**, **27**, and **30** and derivatives of compounds **13**, **14**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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