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Diastereoselective Synthesis of the *Cis*-Octahydronaphthalene Nucleus of Superstolides A and B

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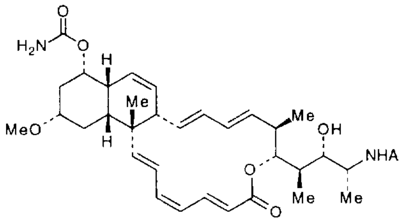
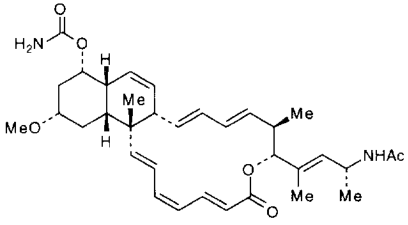
Abstract: A highly diastereoselective synthesis of ***4*** *via the intramolecular Diels-Alder reaction of trienal* ***3*** *is described.* Copyright © 1996 Elsevier Science Ltd

Superstolides A (**1**) and B (**2**), a pair of structurally novel 16-membered macrolides, were isolated from the New Caledonian sponge *Neosiphonia superstes* by Minale and coworkers in 1994.[1,2] Both of these macrolides have been shown to be highly cytotoxic against cancer cell lines such as murine P388 leukemia cells (IC_{50} = 0.003 μg/mL for **1** and **2**), human nasopharyngeal cells (0.005 μg/mL for **2**), non-small-cell lung carcinoma cells (IC_{50} = 0.04 μg/mL for **1** and **2**). We were attracted to the possibility that the octahydronaphthalene nuclei of **1** and **2** (e.g., **4**) could be assembled with high stereoselectivity by the intramolecular Diels-Alder (IMDA) reaction of trienal **3**.[3,4] However, while the diastereochemical course of IMDA reactions leading to *trans*-fused octahydronaphthalenes has been extensively studied and is now well understood,[5-8] much less is known about the diastereoselectivity of IMDA reactions leading to *cis*-fused octahydronaphthalenes, particularly in cases where the dienophile activating group is at the terminal position as in **3**.[9] There is also the issue of endo vs. exo cycloaddition, which is influenced by non-bonded interactions involving remote substituents[10] and the degree of twist asychronicity of the competing transition states, which in turn is related to the extent of dienophile activation.[11] More to the point, prior to this work we were unaware of any examples of IMDA reactions of 2(Z),8(E),10(E)-undecatrienals. However, by analogy to the IMDA reactions of 2(Z),8(E),10(E)-undecatrienoates we expected that excellent selectivity for the cis-fused diastereomer would be achieved by using Lewis acid catalysis.[12,13] We are very pleased, therefore, to report herein a highly diastereoselective synthesis of **4** via the intramolecular Diels-Alder reaction of (Z,E,E)-trienal **3**.

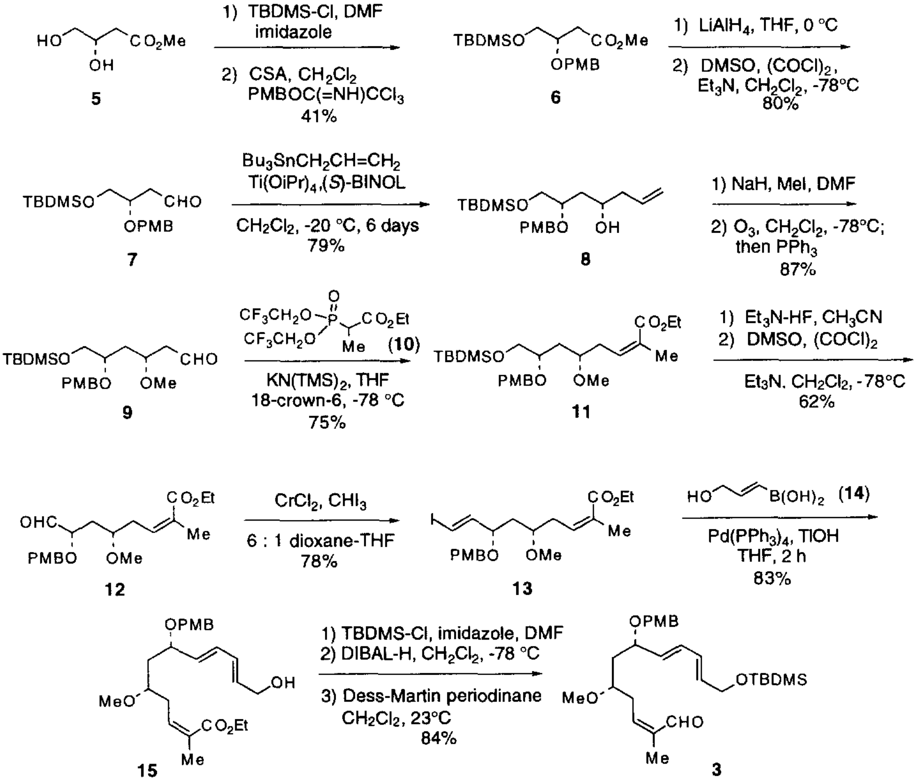


1

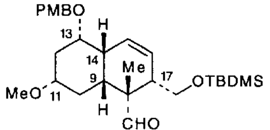


2

Our synthesis of trienal **3** commenced with a standard two-step protection of diol **5**, derived from dimethyl (S)-maleate.[14,15] Reduction of **6**[16] with $LiAlH_4$ (THF, 0°C) and Swern oxidation (DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C) of the derived alcohol then provided aldehyde **7** in 80% yield.[17] We planned originally to prepare the 1,3-syn diol **8** via the double asymmetric allylboration of β-alkoxy aldehyde **7** with the diisopropyl (R,R)-tartrate modified allylboronate reagent.[18] This proved to be a mismatched reaction that provided **8** with only ca. 3 : 1diastereoselectivity (THF, -78°C). Much better results were obtained by using the catalytic asymmetric allylstannation protocol developed by Keck, which provided **8** with 94 : 6 diastereoselectivity (79% yield).[19] After formation of the methyl ether (96%) and ozonolysis of the vinyl group (91%), aldehyde **9** was elaborated to the (Z)-enoate **11** via Still's modification of the Horner-Wadsworth-Emmons reaction (75%).[20] Cleavage of the TBDMS ether (Et_3N-HF, CH_3CN) and Swern oxidation of the resulting alcohol provided aldehyde **12** (62%), which was elaborated to the (E)-vinyl iodide **13** by using the Takai olefination protocol (CHI_3, $CrCl_2$, 6 : 1 dioxane-THF, 78% yield).[21,22] Suzuki cross coupling of **13** with 2 equiv. of vinylboronic acid **14**[23] (0.1 equiv. $Pd(PPh_3)_4$, THF, aq. TlOH) provided **15** in 84% yield,[24,25] which was then elaborated to trienal **3** by protection of the primary alcohol as a TBDMS ether (99%), DIBAL reduction of the carbomethoxyl group (2.5 equiv., CH_2Cl_2, -78°C, 87%) and Dess-Martin periodinane oxidation[26] of the primary allylic alcohol (98%). The overall yield of **3** was 84% for this three step sequence.

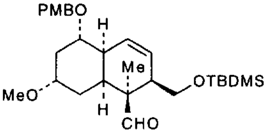


Heating a 0.1 M solution of **3** in toluene at reflux for 22 h provided a ca. 6 : 2 : 1 mixture of three IMDA cycloadducts (**4**, **16**, and **17**, respectively) in 63% yield. The stereochemistry of the major product was assigned as **4** on the basis of two key ^1H-^1H coupling constants ($J_{9,14}$ = 3.5 Hz and $J_{13,14}$ = 4.6 Hz) and NOE interactions between H(9), H(11), H(13) and H(14). In addition, irradiation of the quaternary methyl group led to NOE enhancements of H(9), H(14) and H(17). The second most predominant product was assigned as the alternative cis-fused diastereomer **16** on the basis of the indicated coupling constant data, as well as NOE by interactions between H(9) and H(14), and between the aldehyde C-H and H(11) and/or H(13). The minor product, **17**, was assigned the trans-fused stereochemistry on the basis of the large coupling constants between H(9)-H(14) and H(13)-H(14), and NOE interactions between the aldehyde C-H and H(14) and H(17), but not H(9). The three cycloadducts are formed via transition states **A**-**C**, respectively.



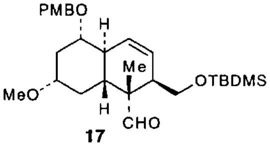
4

$J_{9,14}$ = 3.5 Hz
$J_{13,14}$ = 4.6 Hz



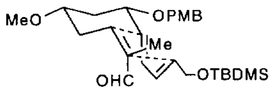
16

$J_{9,14}$ = 6.9 Hz
$J_{13,14}$ = 9.8 Hz

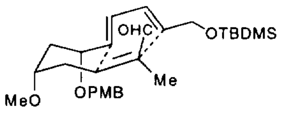


17

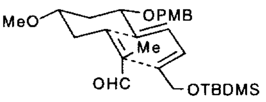
$J_{9,14}$ = 12.2 Hz
$J_{13,14}$ = 10.6 Hz



t.s. **A**



t.s. **B**



t.s. **C**

Unfortunately, attempts to improve the selectivity of this IMDA reaction by using Lewis acid catalysts were unsuccessful. No reaction occurred when **3** was treated with Me_2AlCl or $EtAlCl_2$ in CH_2Cl_2 at -78°C. Cycloadduct **4** was obtained, but in poor yield, when the cyclization was performed at 0°C in the presence of Et_2AlCl; with this reagent at -78°C, ethylation of the aldehyde was the major pathway. Evidently, the carbonyl group of the (Z)-enal is sufficiently hindered that the rate of the Lewis acid catalyzed IMDA reaction is much slower than for (E,E,E)-2,8,10-undecatrienals, which are excellent substrates for this reaction.[5,6,11,27,28] The IMDA reaction was accelerated when performed in the presence of 0.2 equiv. of $Yb(fod)_3$ (toluene, reflux; 1 h vs. >20 h in the absence of the lanthanide catalyst),[29] but with no change in selectivity compared to the uncatalyzed reaction. Ultimately, improved diastereoselectivity was realized by performing the IMDA reaction of **3** in CF_3CH_2OH (0.1 M, 80°C, 20 h), which provided a 10 : 1 : 1 mixture of **4**, **16** and **17**, respectively, in 76% combined yield. The yield of **4** purified chromatographically was 60%. The improved selectivity of this reaction does not appear to be the consequence of Lewis acid catalysis, since the overall ratio of endo : exo products (e.g., (**4** + **16**) : **17**) was virtually unchanged (89 : 11 for the reaction in toluene vs. 92 : 8 in CF_3CH_2OH). Rather, the improved ratio of products is the consequence of increased discrimination between transition states **A** and **B**, giving rise to **4** and **16**, respectively. We speculate that this may be due to increased solvation of the C(11) and C(13) alkoxy groups via hydrogen bonding with the solvent, thereby effectively increasing the magnitude of the 1,3-diaxial interaction between the two groups in transition state **B**.[30,31]

In conclusion, a highly diastereoselective synthesis of cis-fused bicycle **4** corresponding to the hydronaphthalene nucleus of the superstolides has been achieved. Further studies on the synthesis of these interesting targets will be reported in due course.

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