Total Synthesis of (+)-Damavaricin D

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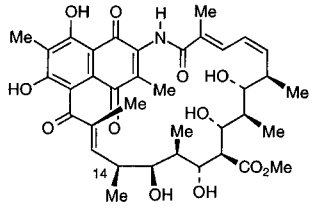
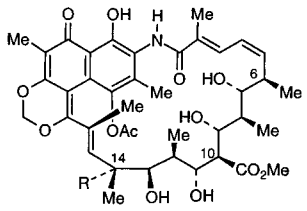
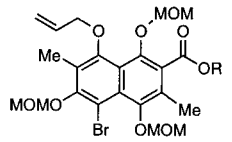
Damavaricin D (DmD, **1**) is both a biosynthetic precursor of the streptovaricin antibiotic family as well as a degradation product of streptovaricin D (SvD).[2,3] The damavaricins, like the streptovaricins, are inhibitors of RNA-directed DNA polymerase (i.e., reverse transcriptase),[4] and certain derivatives have other interesting biological properties.[5] The stereochemistry of **1** has been assigned on the basis of its biosynthetic conversion into streptovaricin C (SvC),[3] the structure and absolute configuration of which have been determined by X-ray analysis of a heavy atom derivative.[6] The only stereocenter of DmD/SvD



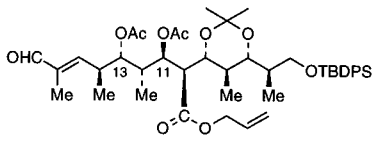
damavaricin D
(**1**, DmD)



streptovaricin C, (SvC, R = OH)
streptovaricin D, (SvD, R = H)



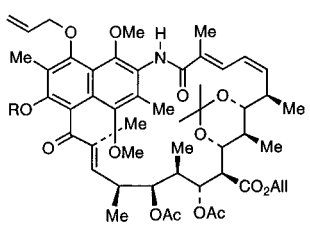
2, R = $CH_2CH_2SiMe_3$



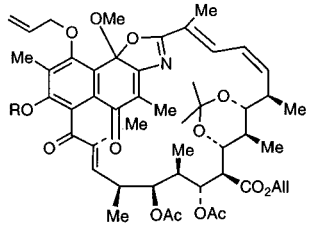
3

not known with certainty prior to our work is C(14). However, the stereochemistry proposed for the C(6)−C(14) segment of DmD/SvD is identical to that found in awamycin.[7] We report herein a total synthesis of damavaricin D, the first synthesis of any member of this family,[8] by a route that utilizes the highly functionalized bromonaphthalene **2** and the ansa chain aldehyde **3**[9,10] as key intermediates.

The successful completion of this synthesis was critically dependent on three issues: (i) use of acetate protecting groups for the C(11,13)-diol;[11] (ii) use of an allyl ester to protect the C(10)-carboxyl of **3**, thereby facilitating removal of the two acetates at the end of the synthesis; and (iii) use of acid labile methoxymethyl (MOM) ethers (see **2**) to protect the 1,4-dihydronaphthoquinone precursors to **1**.[10] Use of phenolic MOM ethers was required by our finding that attempted oxidative demethylation of **4** (and related intermediates) provided **5** which could not be elaborated to DmD.[10] This necessitated that the 1,4-dihydronaphthoquinone deprotection and oxidation steps be decoupled.



4, R = MOM



5, R = MOM (unstable)

Acid hydrolysis of **6**[10,12] and reprotection of the phenol as a *tert*-butyldiphenylsilyl (TBDPS) ether provided **7** (87% yield) (Scheme 1). This protecting group switch was required because bromination of **9** was possible only when the C(19) phenol was unprotected. Dithionite reduction of **7**[13] followed by in situ protection of the air-sensitive hydroquinone with MOM-Cl and 50% aqueous NaOH under phase transfer conditions provided **8** in 82% yield. Carboxylation of the aryllithium intermediate generated from **8** followed by Mitsunobu esterification[14] of the naphthoic acid with β-(trimethylsilyl)ethanol provided **9** in 75% overall yield. Finally, removal of the TBDPS ether, bromination of C(18) with *N*-bromosuccinamide (NBS), and reprotection of the phenol as a MOM ether provided **2**.

Metallation of **2** (1.8 equiv) with *n*-BuLi (1.5 equiv) in THF at −100 °C followed by addition of enal **3** (1.0 equiv) provided a mixture of allylic alcohols (83%) that was oxidized with the Dess−Martin periodinane to give enone **10** in 94% yield as a 1:1 mixture of atropisomers (Scheme 2).[15] After deprotection of the TBDPS ether (Et_3N−HF, CH_3CN, 89%),[16] the primary alcohol was oxidized via the Swern protocol[17] and the aldehyde chain extended via Still's (*Z*)-selective olefination procedure,[18] thereby providing **11** in 72% yield along with 5% of the (*E*)-olefin isomer. The carbamate functionality of **12** was then introduced in 66% yield via a Curtius reaction[19] of the carboxylic acid generated by tetrabutylammonium fluoride mediated deprotection of **11**.[20]

Selective reduction of the (*Z*)-enoate unit of **12** required careful control of the reaction conditions to prevent competitive reduction of the C(11) and C(13) acetates. Treatment of **12** with 5 equiv of diisobutylaluminum hydride (DIBAL-H) in THF at −100 to −78 °C for 1.5 h provided the (*Z*)-enal **14** (14%), (*Z*)-allylic alcohol **13** (33%), and recovered **12** (49%). After

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(11) The crotylchromium addition used to establish the C(11,12) bond in our inital approach (ref 9) could not be scaled up. Ultimately, the C(11,-12) bond was constructed with excellent stereoselectivity via a crotylboration sequence *after* first reducing the C(10)-acyl unit to a -CH_2OH group. Subsequent reoxidation of this substituent proceeded with acceptable efficiency only when C(11)-OH was protected as an acetate (ref 10). Full details of the synthesis of **3** are provided in the Supporting Information.

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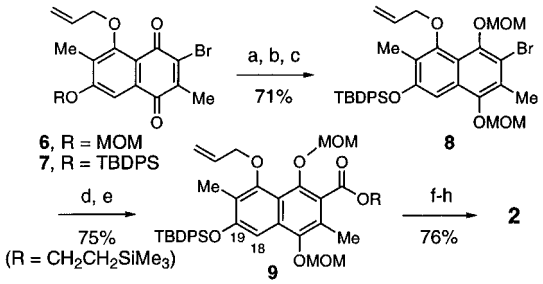
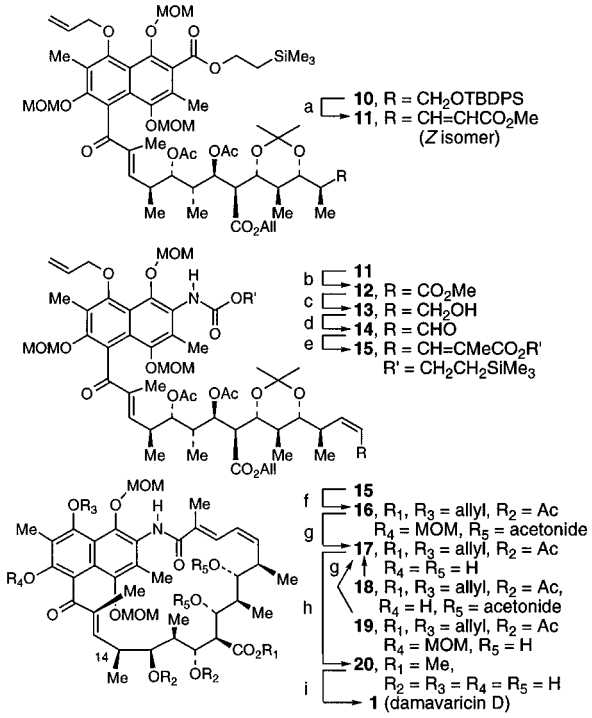
Scheme 1



(a) *p*-TsOH, MeOH, CH_2Cl_2, reflux; (b) TBDPS-Cl, imidazole, DMF; (c) $Na_2S_2O_4$, Adogen 464, CH_2Cl_2-H_2O; then NaOH, MOM-Cl; (d) *n*-BuLi, THF, -78 °C, then CO_2; (e) DEAD, Ph_3P, $TMS(CH_2)_2OH$, THF; (f) Et_3N-HF, CH_3CN; (g) NBS, $CHCl_3$; (h) MOM-Cl, *i*-Pr_2NEt, CH_2Cl_2

Scheme 2



(a) *(i)* Et_3N-HF, CH_3CN (89%); *(ii)* $(COCl)_2$, DMSO, Et_3N, -78 °C; *(iii)* KHDMS, 18-crown-6, $(CF_3CH_2O)_2POCH_2CO_2Me$, THF, -78 °C (72%). (b) (*i*) TBAF, DMF; (*ii*) Ph_2PON_3, Et_3N, $Me_3SiCH_2CH_2OH$, THF (66%). (c) DIBAL, THF, -100 to -78 °C (see text); (d) $(COCl)_2$, DMSO, Et_3N, -78 °C, 67% from **12**. (e) LiCl, DBU, $(EtO)_2POC(Me)CO_2CH_2CH_2SiMe_3$ (86%). (f) (*i*) TAS-F, DMF, (*ii*) *N*-methyl-2-chloropyridinium iodide, Et_3N, CH_2Cl_2 (76%). (g) 1 N HCl-THF (7 : 9), 23 °C, 14 h; 3 recycles of **16**, **18** and **19** (54%). (h) (*i*) $(Ph_3P)_4Pd$, Bu_3SnH, HOAc; (*ii*) LiOH, 2 : 2 : 1 THF-MeOH-H_2O; (*iii*) Me_3SiCHN_2 (50%). (i) 9 : 1 TFA-H_2O, then O_2 (70%).

recycle of **12** (5 equiv of DIBAL-H, −100 to −78 °C, 1 h; then −60 °C for 30 s), **13** and **14** were obtained in 62 and 16% aggregate yields, respectively. Allylic alcohol **13** was oxidized by using the Swern protocol, giving **14** (82%), which was further elaborated to the (*E*,*Z*)-dienoate **15** by a Horner−Wadsworth−Emmons reaction (86%).[21,22] The carbamate and dienoate protecting groups were removed in a single operation by treatment of **15** with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) in DMF.[23] The crude seco acid underwent smooth macrolactamization by using the Mukaiyama salt protocol,[24,25] giving macrolactam **16** in 76% yield from **15**. Although all intermediates from the stage of **10** through **15** were ca. 1:1 mixtures of atropisomers, macrocycle **16** was a single atropisomer by ^1H NMR analysis.[26]

With **16** in hand, we anticipated that the DmD synthesis would be completed in a straightforward manner since the remaining deprotection steps had been developed using **4** and **9** as substrates.[10] However, **4** proved to be a uniquely poor model for **16,** since the two macrocycles exist in opposite atropisomeric series[27] and the reactivity of **16** was substantially different than that of **4**.[28] Both **4** and **16** exist in thermodynamic wells (as determined by variable temperature ^1H NMR studies); why this pair of structurally similar compounds exhibit such strikingly different conformational properties and reactivity remains a mystery. Ultimately, a successful deprotection sequence was developed as follows. Hydrolysis of **16** in a two-phase mixture of 1 N HCl and THF (7:9) at 23 °C for 14 h provided a mixture of diol phenol **17**, phenol acetonide **18**, diol **19**, and recovered **16**. Resubjection of **16**, **18**, and **19** to these conditions (three recycles) provided **17** in 54% yield. The phenolic allyl ether and the C(10) allyl ester of **17** were removed by using catalytic $(Ph_3P)_4Pd$ and *n*-Bu_3SnH in toluene containing HOAc.[29] Treatment of the resulting C(10)-carboxylic acid with excess LiOH in 2:2:1 THF−MeOH−H_2O, followed by esterification with Me_3SiCHN_2,[30] effected clean removal of both acetate protecting groups and provided **20** in 50% overall yield. Finally, hydrolysis of **20** with 9:1 TFA−H_2O in CH_2Cl_2 and air oxidation of the resulting hydroquinone provided totally synthetic (+)-damavaricin D in 70% yield. The identity of the synthetic material was determined by comparison with an authentic sample of the natural product kindly provided by Prof. Rinehart.

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Supporting Information Available: Experimental procedures (including procedures for the synthesis of the ansa chain aldehyde **3**) and characterization data for all new compounds (54 pages). See any current masthead page for ordering and Internet access instructions.

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(27) Rinehart has argued that the major contribution to the optical rotations of the streptovaricins and damavaricins is the helicity of these molecules, since all natural Sv's and Dm's have positive rotations, whereas all of the known atropisomers have negative rotations (see refs 3 and 26). On this basis, macrocycles **16** ($[\alpha]^{25}_D$ +85.7°) and **4** ($[\alpha]^{25}_D$ −10.0°) are believed to be in the natural and unnatural atropisomeric series, respectively.
(28) Attempted deprotection of the acetonide and MOM ethers of **16** with *p*-TsOH in MeOH gave a complex mixture of products, whereas the analogous treatment of **4** provided the corresponding dihydroxy phenol in 93% yield. Similarly, attempts to remove the allyl and acetate protecting groups of **16** by using $(Ph_3P)_4Pd$ and dimedone followed by LiOH resulted in total decomposition, whereas the analogous deprotection sequence was successfully performed on **4**.
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