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SYNTHESIS AND CRYSTALLOGRAPHIC ANALYSIS OF A BICYCLIC CORE RELATED TO THE ESPERAMICIN/CALICHEMICIN AGLYCONES

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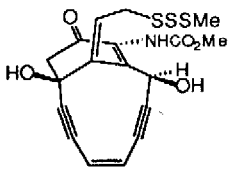
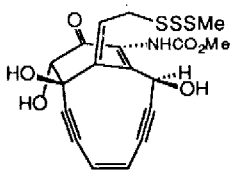
Abstract The synthesis and crystallographic analysis of a bicyclic core related to the esperamicin/calichemicin aglycones is reported. A key reaction involves the skeletal rearrangement of a mesylate derived from a type II Diels-Alder cycloadduct.

The DNA damaging natural products calichemicin γ_1 and esperamicin A_1 have attracted considerable attention.[1,2] Since the initial discovery of these agents, reports have appeared relating to their reactivity,[3] interactions with DNA,[4,5] and chemical synthesis.[3,6] This Letter describes a novel synthetic route to a bicyclic core related to the aglycone (**1**, **2**) of these natural products. An isomeric skeleton, obtained from a type II Diels-Alder reaction,[6d] is shown to undergo a Tsuchihashi-pinacol rearrangement with concomitant and diastereoselective acyloin shift to provide the natural ring system.



1 calichemicin γ_1 aglycone



2 esperamicin A_1 aglycone

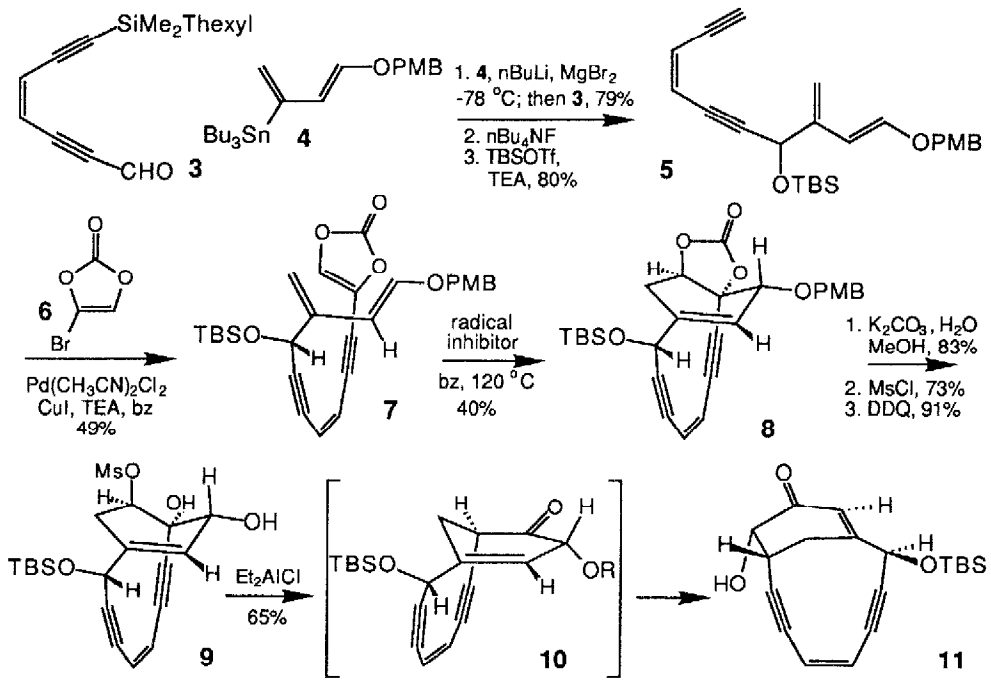
Our recent reinvestigation of the type II Diels-Alder cycloaddition of core precursors provided the expectation that an isomeric skeleton would result from this type of reaction.[6d] Accordingly, diene and dienophile substituents were sought that would facilitate a subsequent skeletal rearrangement to the desired ring system. The implementation of this strategy is shown in the Scheme.

The readily available aldehyde **3**[7] was coupled to a vinyl lithium reagent prepared by transmetallation of vinyl stannane **4**[8] with n-butyllithium (THF, -78 °C). Silyl group transposition was achieved by removal of the acetylenic trialkylsilane with tetra n-butylammonium fluoride (THF, 0 °C) followed by silylation of the alcohol function with t-butyldimethylsilyl triflate and triethylamine (CH_2Cl_2, 0 °C) to provide **5**. A transition metal catalyzed coupling[9] of bromovinylene carbonate **6**[10] was found to proceed in good yield with systems related to **5**; however, with the diene substitution pattern of this particular substrate a more modest yield of product **7** was obtained. This reaction was found to be sensitive to the choice of palladium catalyst.

When heated in the presence of Kishi's radical inhibitor,[11] compound **7** underwent cycloaddition with excellent diastereoselectivity (β/α = 20:1) and the anticipated "para" bridged regioselectivity[6d] to provide

8.[12] Saponification of the cyclic carbonate, selective mesylation of the secondary alcohol, and removal of the p-methoxybenzyl protective group[13] provided the "pinacol substrate" **9**.

Scheme



Recently, Tsuchihashi and co-workers have reported mild reaction conditions to achieve pinacol rearrangements that utilize a Lewis acid and a monomesylate of a vicinal-diol.[14] In these studies, the acetylene function failed to undergo migration.[15] In the case at hand, treatment of **9** with six equivalents of diethylaluminum chloride (CH_2Cl_2, -78 °C, 2h then -78 °C to -20 °C, 2h) delivered the enone **11** with the same relative stereochemistry as observed in esperamicin at the carbinol center (>15:1, 65% yield). Although the stereochemistry of this reaction is consistent with the migration of the allylic hydrogen in concert with the shift of the acetylene, the detection of an intermediate (IR 1735 cm^{-1}) suggests the occurrence of an alternative process[16] involving the acyloin isomer (**10**, R=H). Enolization of the initially formed acyloin would produce an enediolate that is expected to protonate on the diastereoface that is opposite to the enediyne bridge.[6c]

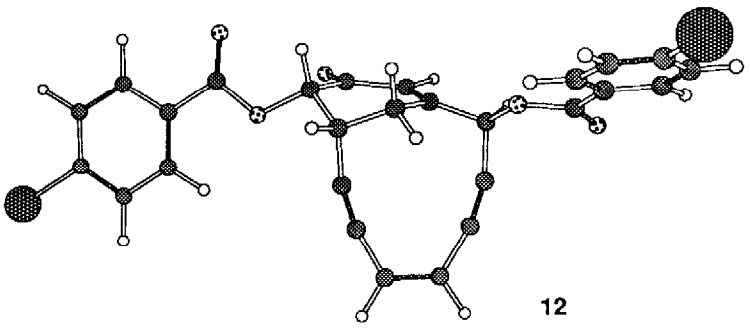
The assignment of structure **11** to the product of the rearrangement followed spectroscopic analysis. A strong absorption in the infrared spectrum at 1680 cm^{-1} and the chemical shift of the α-vinylic hydrogen at δ 6.03 in the ^1H NMR spectrum were diagnostic of an α,β-unsaturated cyclohexenone. The magnitude of spin-spin coupling constants was consistent only with the α-stereochemistry at the carbinol site.[17]

Confirmation of the proposed structure was obtained following X-ray crystallographic[18] analysis of the bis(p-bromobenzoate) derivative of **11** ((i) HF, CH_3CN (79%), (ii) p-bromobenzoyl chloride, TEA, CH_2Cl_2, 0 to 25 °C (65%)). The x-ray analysis revealed the molecular structure shown in the Figure (**12**). The three independent molecules in the asymmetric unit had, within experimental error, identical core

geometries and only one of them is shown. The geometries of the triple bonds show marked deviations from linearity, as has become to be expected for this structural class.[6c] Averaged over the twelve independent observations in this analysis, the bond angle at an acetylenic carbon was 167.1(20)°, and the distortion seems greatest at the carbon adjacent to the secondary hydroxyl where the mean angle is 164.4(2)°. In contrast, the double bonds do not appear to have suffered significant distortions from ideal geometry and have a mean angle of 119.6(9)°. The distortion of the acetylenic bonds reduces the distance between the terminal acetylenic carbons to 3.46(2) Å while the undistorted distance is reported to be 4.17 Å.[19]

Current investigations are focussed on (*inter alia*) variations of the rearrangement reaction in order to deliver the specific target molecules of our research efforts.

Figure



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17. **11**: *^1H NMR* (500 MHz, $CDCl_3$) δ 6.03 (d, J=2.5 Hz, 1H, RR^1C=CH-), 5.83 (dd, J=9.5, 2.4 Hz, 1H, -CH=CH-C≡C-CH(OTBS)-), 5.78 (dd, J=9.5, 1.3 Hz, 1H, -CH=CH-C≡C-CH(OTBS)-), 5.20 (br s, 1H, -CH(OTBS)-), 4.37 (d, J=5.4 Hz, 1H, -CH(OH)-), 3.85 (br s, 1H, -OH), 3.81 (m, 1H, RR^1CH-C≡C-), 3.28 (dd, J=16.3, 2.6 Hz, 1H, -CHH-), 2.84 (ddd, 16.3, 3.3, 2.6, Hz, 1H, -CHH-), 0.92 (s, 9H, $-C(CH_3)_3$), 0.18 (s, 3H, $-SiCH_3$), 0.14 (s, 3H, $-SiCH_3$); Selected decoupling (500 MHz, $CDCl_3$): Irradiation at δ 2.84, simplification at δ 3.28, 3.81, and 6.03. Irradiation at δ 3.28, simplification at δ 2.84, 3.81 and 6.03 (slight). Irradiation at δ 5.83, 5.78 (simultaneous), simplification at δ 3.81, 5.20; *^{13}C NMR* (62.9 MHz, $CDCl_3$) δ 197.2, 164.6, 125.5, 122.2, 121.1, 99.2, 98.4, 88.7, 83.4, 74.9, 67.4, 39.6, 34.0, 25.7, 18.2, -4.5, -4.9; *IR* (film) ν 3480 (br), 1680 (s) cm^{-1}; *HRMS* (CI, isobutane) calculated M+ 329.1573, observed M+ 329.1563.
18. Compound **12** (mp >100 °C (dec)) crystallized in the triclinic space group P1bar with **a** = 13.577(10), **b** = 15.212(5), **c** = 18.712(6)Å, α = 77.13(3)°, β = 86.27(5)°, γ = 70.45(5)° and *three* independent molecules in the asymmetric unit (Z = 6). Intensity data were collected on a computer controlled four-circle diffractometer using Cu Kαbar radiation (1.54178 Å) and variable speed 2θ:θ scans. A total of 7307 reflections were collected, and 5430 (74%) were judged observed ($|F_O| \geq 3\sigma(F_O)$) after correction for Lorentz, polarization, and background effects. The structure was solved uneventfully by a combination of heavy atom and tangent formula recycling procedures. Blocked full-matrix least-squares refinements with anisotropic heavy atoms and isotropic riding hydrogens have converged to a conventional crystallographic residual of 0.0725 for the observed reflections. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.) Please provide a complete literature citation when ordering.
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