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Intramolecular diyl trapping reactions en route to the bicyclo [3.2.1] framework; an approach to aphidicolin

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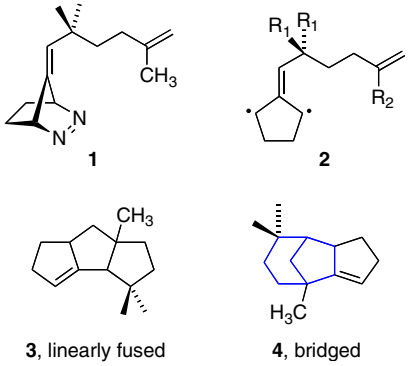
ABSTRACT

We describe an application of the intramolecular diyl trapping cycloaddition reaction to the assembly of the bicyclo [3.2.1] framework, and utilize the outcome to complete a formal total synthesis of aphidicolin.

The trimethylenemethane diyl (TMM) made its first appearances in the literature in 1948 and 1950.[1] Longuet-Higgins prediction that: 'alternate hydrocarbons with no classical structure of the K-type should be paramagnetic in the ground state',[2] provided an apropos description of TMM. Years later, Dowd reported the first synthesis and ESR spectral characterization of TMM.[3] A report from his group appearing in 1976 established unambiguously that TMM does possess a triplet ground state, as predicted.[4] Berson et al. initiated a detailed and systematic investigation of the reactivity of cyclopentadiyls of the TMM variety, with their first reports appearing in 1971.[5] We entered the field with a publication describing the use of an intermolecular cycloaddition that we refer to as a 'diyl trapping reaction', to construct the linearly fused tricyclopentanoid framework that is common to a host of bioactive natural products.[6] Through the efforts of many, the reactivity pattern for TMM diyls has emerged.[7] Thus, in addition to both intermolecular and intramolecular cycloaddition, the diyls can engage in atom transfer processes,[8] cut DNA,[9] and undergo several interesting fragmentation–recombination processes.[10]

A striking observation made by Carroll and Little in 1981[11] was that the intramolecular cycloaddition of the diyl derived from diazene **1** led to the formation of an approximately 1:1 mixture of the linearly fused and bridged cycloadducts, **3** and **4**, respectively. Prior to that time, only the linear pathway had been observed. Eventually, we learned how to generate either skeletal type by design, and have formulated the following simple guidelines: (a) linearly fused cycloadducts arise in those instances where an electron-withdrawing group is appended to either of the sp^2-hybridized carbons of the diylophile (note structure **2**), (b) in contrast, the positioning of an alkyl group on the internal carbon of the diylophile leads preferentially to the bridged framework, and (c) the larger the group (e.g., $R_2 = CH_3$ vs $CH(OR)_2$ vs $C(OR)_2CH_3$), the greater the preference.[7]



1 **2**

3, linearly fused **4**, bridged

The ability to gain access to either framework intrigued us sufficiently to wonder whether TMM diyl chemistry could be applied to the synthesis of a natural product wherein the bicyclo [3.2.1] subunit that is found in the bridged adducts constituted an

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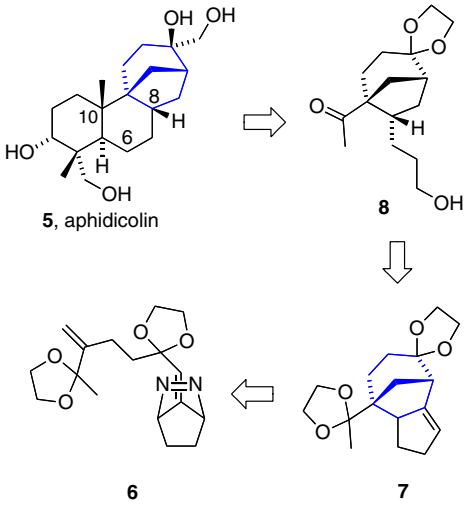
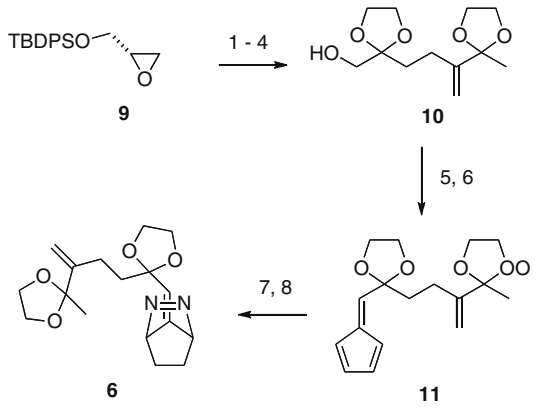
important structural feature of the target. To explore this notion, we set our sights upon the anti-tumor agent aphidicolin (**5**).[12] It has long been the focus of practitioners of total synthesis, and their efforts have led to notable achievements.[13] We selected diazene **6** as the diyl precursor of interest. If our guidelines are correct then the presence of the large hetero-alkyl substituent appended to the diylophile will ensure the preferential formation of the bridged framework. Once formed, our plan calls for an oxidative cleavage of the C–C π-bond in **7** and the selective conversion of one of the two ketals to the methyl ketone found in structure **8**. We focus upon structure **8** since it has previously been converted to the natural product,[13m] and because it presents a challenging [3.2.1] framework upon which to apply the diyl chemistry and test our guidelines. We describe our results herein.

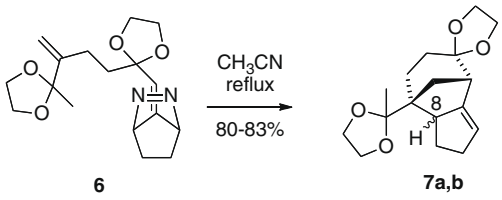


Diazene **6** was assembled via a sequence that began with the silyl ether **9** of glycidol (Scheme 1). Ring opening of the epoxide was accomplished using the dianion of 3-methyl-3-buten-2-ol. Subsequent Doering–Parikh oxidation followed by installation of the ketal units and desilylation provided an efficient route to structure **10**.[14] A Swern oxidation followed by reaction with sodium cyclopentadienide delivered fulvene **11**.[15] Diimide reduction of the Diels–Alder adduct formed via the reaction of **11** with bis(2,2,2-trichloroethoxycarbonyl) azo dicarboxylate set the stage for conversion of the biscarbamate unit to the diazene linkage. This was most efficiently accomplished electrochemically using a controlled potential electrolysis at a potential of −1.65 V (vs Ag/AgCl).[16] Oxidation of the resulting hydrazine using cupric chloride delivered diazene **6**. This protocol proved to be superior to the use of saponification followed by a ferricyanide oxidation and further highlights the utility of electrochemistry.[17]

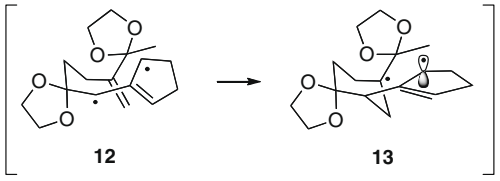


Scheme 1. Reagents and conditions: (1) *n*-BuLi, Et_2O, TMEDA; 3-methyl-3-buten-2-ol, Et_2O, then add epoxide **9** in THF (91–93%); (2) SO_3–pyridine, DMSO, TEA, DCM (88–95%); 3. $HOCH_2CH_2OH$, *p*-TsOH, $PhCH_3$ (87–90%); (4) 1 M TBAF, THF (80–83%); (5) Swern; and then (6) 60% NaH, CpH, THF (68–79%, two steps); (7) $(Cl_3CCH_2O_2CN{=})_2$, DCM then $(KO_2CN{=})_2$, AcOH (80–85%); (8) −1.65 V (vs Ag/AgCl, Hg/Mg), DMF; $CuCl_2$ (90%).

With diazene **6** in hand, the stage was set to convert it to the TMM diyl and therefore, to test the utility of our guidelines. The intramolecular diyl trapping reaction was initiated simply by refluxing a 2 mM solution of diazene **6** dissolved in acetonitrile.[18] Once TLC analysis showed that the starting material had disappeared, the reaction mixture was cooled to room temperature and the solvent was removed. We were pleased to discover the formation of the bridged cycloadduct as the major product, thereby adding validity to the predictive power of our guidelines. Chromatographic separation of the ~10:1 mixture of bridged to linearly fused cycloadducts led to the isolation of the desired bridged framework **7a**,**b** in 80–83% yields.[19] In addition to possessing the primary structural features of the C,D ring system of the natural product, one finds embedded within **7a**,**b** the carbons destined to become carbon numbers 5-10, as well as the C-10 angular methyl (natural product numbering).

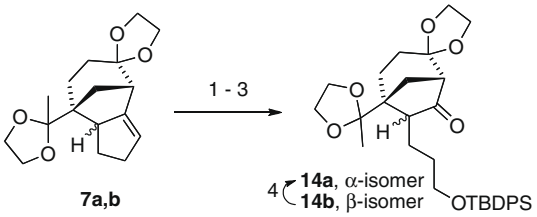


While the yield was high, we were disappointed by the formation of diastereomers at C-8. This outcome is likely to be a consequence of the stepwise nature of the cycloaddition arising from the triplet diyl. Undoubtedly, the first bond is formed via a 6-endo trig cyclization of diyl **12** leading to **13**. Sigma bond formation at either the top or the bottom face of the resulting allylic framework in **13**, accounts for the stereochemical outcome.

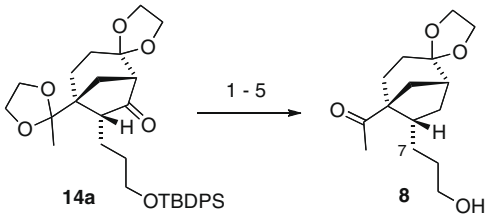


Having established the utility of the intramolecular diyl trapping reaction for the assembly of the [3.2.1] skeleton, we proceeded to convert the cycloadducts to structure **8**, an aphidicolin convergent point.[13m] Toward that end, ozonolytic cleavage of the π-bond in **7a**,**b**, followed by a reductive workup, selective protection of the primary hydroxyl group, and oxidation using PCC/Celite afforded a 1:1 mixture of diastereomeric ketones **14a**,**b**. Once the desired epimer was identified,[20] the unwanted form **14b** was converted to a 1:3 mixture of **14a** to **14b** upon treatment with DBN and pyridine; the isomers were then separated, and the desired form was carried forward. Clearly the need to effect epimerization is a shortcoming of our pathway[21] (Scheme 2).

To complete the sequence, we elected to reduce the ketone and convert the resulting alcohol to a xanthate ester prior to affecting a



Scheme 2. Reagents and conditions: (1) (a) O_3, MeOH/DCM, −78 °C; (b) $NaBH_4$, MeOH/H_2O, reflux; (2) TBDPSCl, TEA, DCM, (70–75% two steps); (3) PCC/Celite, DCM (>98%); (4) DBN, pyr CH_2Cl_2, reflux (1:3 **14a** to **14b** after 6 h), then combine materials and recycle.



Scheme 3. Reagents and conditions: (1) $NaBH_4$, MeOH (99%); (2) (a) NaH; CS_2; MeI, THF (91%); (3) (n-Bu)$_3$SnH, AIBN, PhH (91%); (4) CSA, acetone (92%); (5) TBAF, THF (89%).

radical initiated cleavage of the C–O bond.[22] Subsequent conversion of the bridgehead ketal to a carbonyl unit was readily achieved using catalytic quantities of CSA in wet acetone. That it reacts in preference to the ketal appended to the 3-carbon bridge is undoubtedly a consequence of the strain release that accompanies the conversion from sp^3 to sp^2 hybridization with the attendant removal of the crowded vicinal quaternary centers. A routine fluoride-induced removal of the silyl group led efficiently to the desired structure **8**. Verification that we had reached the convergent point in our synthetic sequence was achieved by comparing our spectral data with those reported in the literature[13m,23] (Scheme 3).

In conclusion, the results reported herein clearly indicate that the intramolecular diyl trapping reaction can indeed be used to assemble the bicyclo [3.2.1] framework that is common to bioactive natural products. The results substantiate the principle that this framework will be produced when the internal carbon of the diylophile is appended with a large alkyl group. Judicious selection of this group allows functional group manipulation once the cycloaddition has been completed.

Acknowledgments

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18. The low concentration is used to assure that triplet dimerization is not competitive with cycloaddition.
19. The ratio of bridged to linearly fused cycloadducts was determined by ^{1}H NMR.
20. The desired epimer was identified by comparing our data with those of Toyota, Nishkawa, and Fukuoto for structure **8**. See Ref. 13m.
21. We suspect, but have not proven, that through additional experimentation a substantially more effective epimerization could be identified. Since the total synthesis was not our major objective, we opted not to explore the options.
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23. *The spectral data for structure* **8**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00–3.83 (m, 4H), 3.65 (t, 1H, J = 6.4), 2.38–2.30 (m, 1H), 2.22–2.17 (m, 1H), 2.15 (s, 3H), 2.14–2.10 (m, 1H), 2.03–1.99 (m, 1H), 1.89–1.76 (m, 3H), 1.68–1.59 (m, 4H), 1.57–1.44 (m, 2H), 1.40–1.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.9, 110.9, 64.6, 64.1, 62.7, 57.1, 43.2, 42.6, 40.4, 32.5, 31.8, 29.4, 26.5, 26.4, 26.1. ESI-MS: found 291.1555, $C_{15}H_{24}O_4Na^+$ Calculated 291.1572. For structure **10**, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.18 (d, 1H, J = 1.0), 4.81 (d, 1H, J = 1.4), 3.96–3.70 (m, 8H), 3.46 (s, 2H, 2.57 (br, 1H), 2.11–2.03 (m, 2H), 1.84–1.75 (m, 2H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 148.5, 109.9, 109.8, 109.2, 65.4, 65.0, 64.1, 33.3, 24.1, 23.8. For fulvene **11**, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.85–6.80 (m, 1H), 6.58–6.53 (m, 1H), 6.47–6.43 (m, 1H), 6.22 (s, 1H), 6.17–6.13 (m, 1H), 5.24 (d, 1 H, J = 1.2), 4.86 (d, 1 H, J = 1.4), 4.02–3.77 (m, 8 H), 2.27–2.17 (m, 2 H), 2.09–1.99 (m, 2H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 148.6, 145.4, 139.1, 134.7, 131.6, 126.3, 121.1, 110.7, 109.3, 64.6, 64.3, 37.8, 24.2. For diazene **6**, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.79 (s, 1H), 5.24 (d, 1H, J = 1.0),

5.16 (s, 1H), 5.11 (s, 1H), 4.83 (dd, 1 H, J = 1.4, 2.8), 3.99–3.76 (m, 8H), 2.14–2.05 (m, 2H), 1.87–1.78 (m, 2H), 1.72–1.63 (m, 4H), 1.46 (s, 3H), 1.26–1.11 (m, 4H), 0.94 (d, 1H, J = 6.8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 148.5, 147.3, 118.1, 109.9, 109.2, 108.6, 72.8, 64.5, 64.4, 64.2, 37.4, 24.2, 21.1, 20.8. For structures **7a**,**b**, ^{1}H NMR ($CDCl_3$, 200 MHz): δ feature peak 5.68 (s, 1H), 5.37 (s, 1H), 3.92–3.76 (m, 20H), 3.10 (m, 1H), 2.60–2.33 (m, 8H), 2.22–2.18 (m, 1H), 2.12–2.05 (m, 3H), 2.00–1.94 (m, 4H), 1.89–1.80 (m, 3H), 1.74–1.64 (m, 7H), 1.59–1.37 (m, 4H), 1.27 (s, 3H), 1.21 (s, 3H). For structure **14a**, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70–7.66 (m, 4H), 7.44–7.35 (m, 6H), 4.03–3.82 (m, 8H), 3.76–3.73 (dd, 1H, J = 6.4), 3.66–3.60 (m, 1H), 2.47 (d, 1H, J = 6.4), 2.33 (d, 1H, J = 8.4), 2.20–2.03 (m, 2H), 1.91–1.64 (m, 6H), 1.58–1.42 (m, 2H), 1.30 (s, 3H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 218.4, 135.6, 135.5, 134.0, 129.4, 127.5, 111.9, 107.9, 64.9, 64.5, 64.4, 64.1, 54.3, 52.6, 50.6, 33.9, 32.8, 31.6, 26.8, 26.7, 25.1, 23.9, 19.9, 19.2.