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Investigations into an Anionic Oxy-Cope/Transannular Conjugate Addition Approach to 7,20-Diisocyanoadociane

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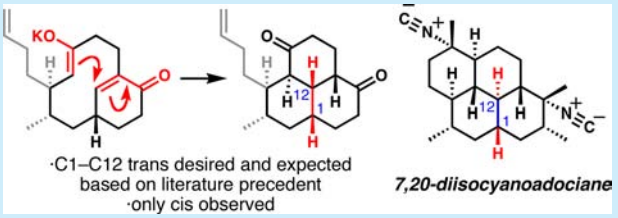
Supporting Information

ABSTRACT: An anionic oxy-Cope/transannular conjugate addition approach to the potent antimalarial 7,20-diisocyanoadociane is presented. The unexpected formation of undesired diastereomers in the key reaction led to the structural reassignment of previous products of this type of cascade and a reevaluation of the reversibility of the transannular ring closure. During efforts to coax the reaction toward the desired product, a transannular ene reaction provided tricyclic compounds relevant to the kempane diterpenoids.



With its attractive saturated, fused, all-chair, all-equatorial tetracyclic structure and its low nanomolar antiplasmodial activity, 7,20-diisocyanoadociane (**1**) is arguably the flagship member of the large family of antimalarial isonitrile-containing diterpenoids (Figure 1).[1−4] The increasing tolerance

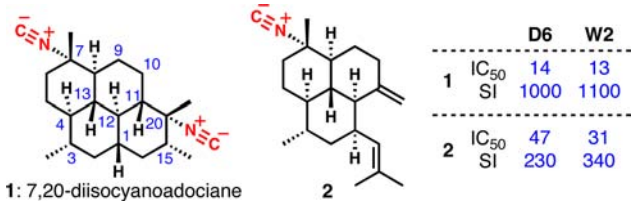


Figure 1. Isonitrile terpenoid activity against *Plasmodium falciparum*; D6 = mefloquine resistant clone; W2 = chloroquine resistant clone; IC_{50} values are in nanomolar; SI = selectivity index with respect to human KB cells (ref 3).

of malaria-causing *Plasmodium* parasites to current treatments necessitates a counteroffensive in the development of new medicinal agents that are preferably complementary to the current state-of-the-art artemisinin combination therapies.[5,6] In this regard, **1** and related amphilectane isonitriles have been underexploited and merit attention.[7,8] Although several groups have contributed syntheses in this series over the past three decades,[9−16] only recently has the first particularly concise route to any member been developed; Pronin and Shenvi's synthesis of amphilectane **2** has set the bar high for these targets.[16] We have initiated a research program targeting these natural products; in this report, we disclose our first efforts toward **1**, which resulted in an unexpected stereochemical outcome in a key transannular Michael addition, and the unanticipated formation of a tricyclic ring system relevant to kempane diterpenoids.

The shortest synthesis of **1** to date, by Corey and Magriotis,[12] arrives at diketone intermediate **3** in 26 steps, which is converted to the natural product via the three operations shown (Figure 2). More direct access to **3** would therefore provide a short formal synthesis of **1**, in spite of the stereochemical complications in the isonitrile introductions.[12]

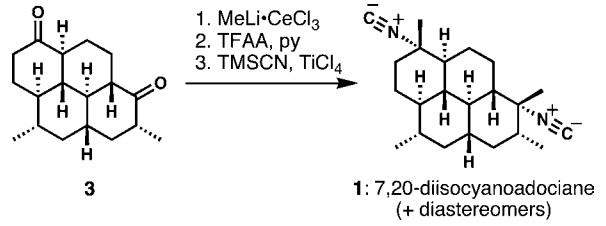


Figure 2. Corey's endgame for 7,20-diisocyanoadociane.

Perusal of the literature concerning fused polycyclic motifs relevant to **1** led us to a report by Swaminathan describing the oxy-Cope/Michael cascade of **4** to **5** (eq 1).[17] On this basis, the use of appropriately substituted spirocycle **6** should afford **7** (eq 2). A sequence of ozonolysis, McMurry coupling, and regioselective hydroboration/oxidation might deliver **3**, thereby completing a short formal synthesis of **1**.

Our efforts began toward C15-desmethyl-**6** (numbering for **1**), which was prepared in similar fashion to Swaminathan's system (Scheme 1). In principle, the missing methyl group could be incorporated at a late stage. Copper-mediated addition of butenylmagnesium bromide to 4-methylcyclohexenone (**8**)[18,19] followed by Robinson annulation afforded spirocycle **10**. Enone protection via formation of the cross-conjugated silyl dienolate and subsequent vinyl addition provided the oxy-Cope precursor **11** as a mixture of diastereomers. Deprotonation of this mixture triggered efficient sigmatropic rearrangement of both diastereomers (>80%, clean conversion). Deprotection

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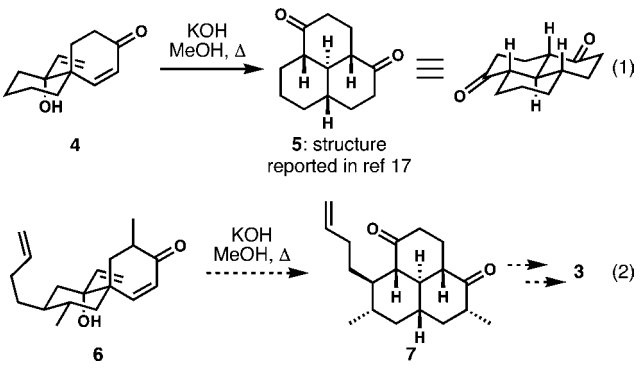
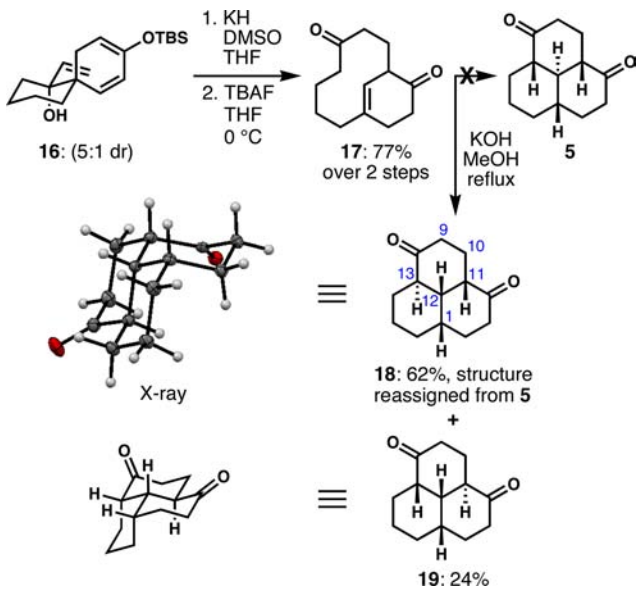


with TBAF revealed the desired δ,ε-cyclodecenone in 51% over two steps. Exposure of **12** to basic methanol effected, as expected, the transannular conjugate addition; however, two compounds **13** and **14** were obtained. Both arise from conjugate addition *cis* to the tether at C4 of the cyclohexenone, and neither contained the desired all-*trans* configuration of **15** that was expected on the basis of the Swaminathan precedent.[17] The observed stereochemical outcome can be explained by indiscriminant protonation of the extended dienolate of **12** to generate diastereomeric conjugated enones followed by selective conjugate addition *cis* to the tethering γ-substituent. Presumably, epimerization of the ring junction tertiary α-carbons is feasible, ensuring the equatorial disposition of the methyl and butenyl groups.

Because the additional substitution in **12** might adversely impact the diastereoselectivity of the conjugate addition,[20−23] we decided to reexamine Swaminathans's original system (Scheme 2). Spirocycle **16** was prepared as above (see Supporting Information) and smoothly underwent anionic oxy-Cope rearrangement to afford **17** after deprotection. At this point, **17** was exposed to basic methanol, which provided a product that generated identical NMR data to those reported by Swaminathan. A second compound not mentioned in the original report was also isolated. Crystals of the literature compound were obtained, and X-ray analysis revealed a critical

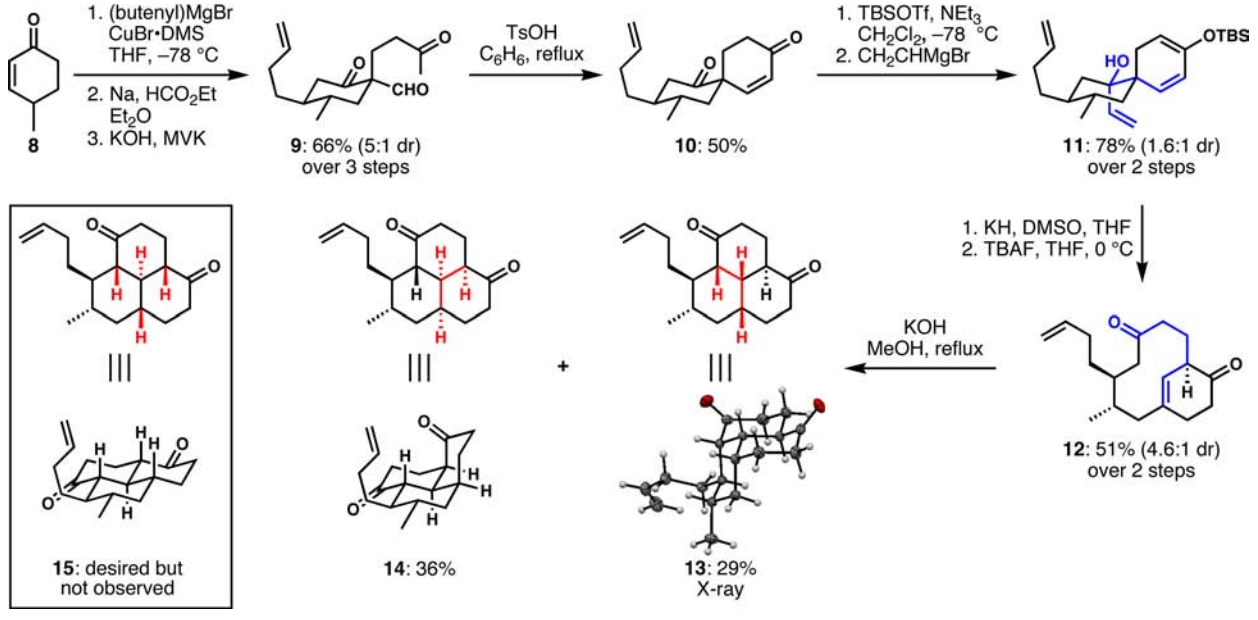
Scheme 2. Reassignment of the Reported Structure 5 (Numbering of 18 Matches 7,20-Diisocyanoadociane)



misassignment. Instead of the proposed all-*trans* perhydrophenalenedione **5**, the observed compound had structure **18**, with a *cis*-relationship between C1, C12, and C11. The second isolated compound, **19**, also bears a *cis* ring fusion (C1−C12) and is epimeric to **18** at C11 and C13.

Because the cyclization of **17** kinetically favors *cis*-addition, we examined the possibility of thermodynamic control to access **5**; however, elevating the temperature and extending the reaction time did not alter the product mixture. In principle, transannular Michael reactions are reversible in the presence of base, because the product 1,5-dicarbonyl can enolize and revert to an enone/enolate pair.[24,25] The all-*trans* perhydrophenalene system is the most stable diastereomer and could theoretically be formed under equilibrating conditions,[26] as put forth by Swaminathan in his assignment of the configuration of his

Scheme 1. Anionic Oxy-Cope/Transannular Michael Addition Stereochemical Outcome



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rearrangement product as **5**.[27] Our observed lack of isomerization brings into question the reversibility of the transannular conjugate addition under these conditions. Understanding the proposed reversibility would provide insight into the feasibility of accessing **5** from **17**.

There are at least two reasonable explanations for the stability of the *cis* ring fusion under equilibrating conditions. First, tricycles **18** and **19** might undergo retro-Michael addition, but only the conformation conducive to *cis*-selective conjugate addition is accessible. Another possibility is that the conjugate addition is simply not reversible under the reaction conditions. These two scenarios can be differentiated by analyzing deuteration at C1 when **18** (or **19**) is treated with deuterated basic methanol (Figure 3).

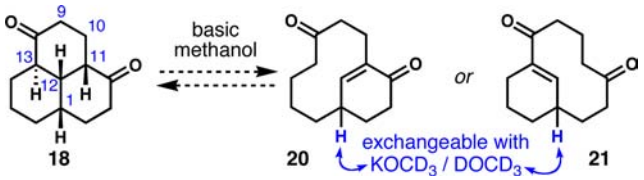
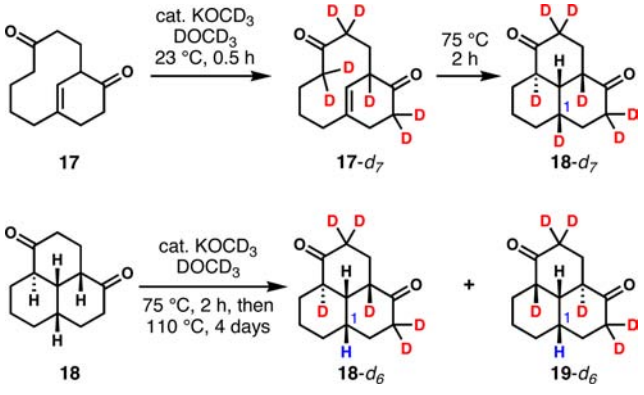


Figure 3. Retro-Michael/Michael equilibrium could promote enolization and exchange at C1.

If the Michael addition is reversible, equilibrating conditions should cause proton exchange of **20** and **21** at C1 before converting back to **18** and **19**, and that could be observed via deuteration experiments. However, if the Michael addition is irreversible under those conditions, **18** will not incorporate deuterium at C1, because this position is not activated for deprotonation.

Three sets of experiments were performed using **17** and **18** (Scheme 3). These experiments were all conducted in a J-Young tube with freshly prepared $KOCD_3$ in CD_3OD and monitored by ^1H and ^{13}C NMR. First, it was determined that **17** is deuterated rapidly at all enolizable positions at room temperature to afford **17**-d_7. Next, heating **17**-d_7 in basic deuterated methanol causes deuteration at C1, affording **18**-d_7. Finally, reacting **18** with basic deuterated methanol under typical reaction conditions—75 °C for 2 h—affords **18**-d_6 and **19**-d_6; no deuteration at C1 was observed. Continued heating at 110 °C for 4 days still does not cause incorporation of deuterium at C1. These results are consistent with a lack of reversibility of the transannular Michael addition.[28]

Scheme 3. Deuteration Experiments To Probe the Reversibility of the Transannular Michael Addition



The failure to convert **12** into **15** in basic methanol at reflux led us to examine its reactivity at much higher temperatures. Instead of the desired conjugate addition to afford **15**, **12** underwent an unexpected transannular carbonyl-ene reaction. Ultimately, we found that heating of enone **22** (obtained by TBAF deprotection of the minor diastereomer of **11**) to 190 °C led to a thermally induced tandem oxy-Cope/carbonyl ene reaction that directly delivered tricyclic product **23** (Figure 4).

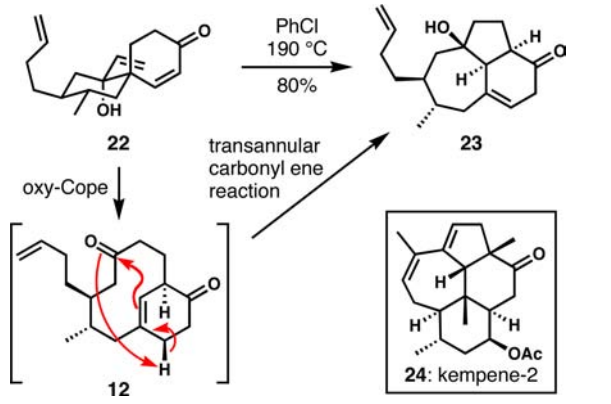


Figure 4. Oxy-Cope/ene approach to a tricyclic ring system relevant to the kempane natural products.

The relative configuration of **23** was assigned as shown because that is the only isomer of the product that can arise via a transannular ene reaction of **12**, and spectral data were consistent with this assignment. This reaction sequence is currently being assessed for an approach to the kempane family of natural products (see **24**).[29,30]

The oxy-Cope/transannular conjugate addition reaction developed by Swaminathan and others is certainly a powerful method for the rapid construction of fused polycylic scaffolds;[31] however, the structural reassignment of **5** to **18** as disclosed in this report leads us to urge caution to other researchers who might aim to make use of several other compounds prepared via similar approaches (**25**–**27**, Figure 5).[17,32,33]

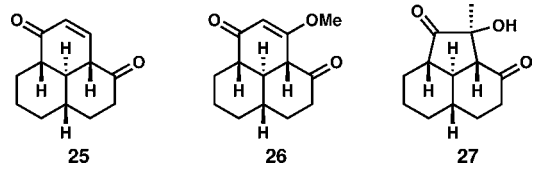


Figure 5. Other literature compounds whose proposed structures might be called into question.

We have disclosed a structural correction to the product of the fascinating oxy-Cope/transannular conjugate addition reaction published by Swaminathan, which we uncovered during our studies toward 7,20-diisocyanoadociane. Instead of an equilibrating process, it appears that a kinetic transannular Michael addition affords a *cis* ring fusion. The reversibility of the transannular addition reaction has been dismissed in this case by deuterium incorporation experiments. During optimization efforts, we obtained access to a fused tricyclic scaffold via an oxy-Cope/ene reaction; this cascade reaction might prove useful in accessing the kempane family of natural products. Our laboratory is continuing work toward the concise syntheses of isonitrile terpenoid natural products.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, including spectra for new compounds, X-ray crystal structures, and CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Garson, M. J.; Simpson, J. S. *Nat. Prod. Rep.* **2004**, *21*, 164.
(2) Wright, A. D.; McCluskey, A.; Robertson, M. J.; MacGregor, K. A.; Gordon, C. P.; Guenther, J. *Org. Biomol. Chem.* **2011**, *9*, 400.
(3) Wright, A. D.; König, G. M.; Angerhofer, C. K.; Greenidge, P.; Linden, A.; Desqueyroux-Faúndez, R. *J. Nat. Prod.* **1996**, *59*, 710.
(4) Baker, J. T.; Wells, R. J.; Oberhänsli, W. E.; Hawes, G. B. *J. Am. Chem. Soc.* **1976**, *98*, 4010.
(5) Dondorp, A. M.; Nosten, F.; Yi, P.; Das, D.; Phyo, A. P.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; Ringwald, P.; Silamut, K.; Imwong, M.; Chotivanich, K.; Lim, P.; Herdman, T.; An, S. S.; Yeung, S.; Singhasivanon, P.; Day, N. P. J.; Lindegardh, N.; Socheat, D.; White, N. J. *N. Engl. J. Med.* **2009**, *361*, 455.
(6) Phyo, A. P.; Nkhoma, S.; Stepniewska, K.; Ashley, E. A.; Nair, S.; McGready, R.; Moo, C. L.; Al-Saai, S.; Dondorp, A. M.; Lwin, K. M.; Singhasivanon, P.; Day, N. P. J.; White, N. J.; Anderson, T. J. C.; Nosten, F. *Lancet* **2012**, *379*, 1960.
(7) Flannery, E. L.; Chatterjee, A. K.; Winzeler, E. A. *Nat. Rev. Microbiol.* **2013**, *11*, 849.
(8) Guantai, E.; Chibale, K. *Malar. J.* **2011**, *10* (Suppl1), S2.
(9) Piers, E.; Llinas-Brunet, M. *J. Org. Chem.* **1989**, *54*, 1483.
(10) Piers, E.; Romero, M. A. *Tetrahedron* **1993**, *49*, 5791.
(11) Piers, E.; Llinas-Brunet, M.; Oballa, R. M. *Can. J. Chem.* **1993**, *71*, 1484.
(12) Corey, E. J.; Magriotis, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 287.
(13) Miyaoka, H.; Okubo, Y.; Muroi, M.; Mitome, H.; Kawashima, E. *Chem. Lett.* **2011**, *40*, 246.
(14) Miyaoka, H.; Okubo, Y. *Synlett* **2011**, 547.
(15) Fairweather, K. A.; Mander, L. N. *Org. Lett.* **2006**, *8*, 3395.
(16) Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 19604.
(17) Rao, C. S. S.; Kumar, G.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1982**, *38*, 2195.
(18) Please see the Supporting Information for the synthesis of (±)-**8**.
(19) Enantioenriched **8** has been used extensively as a starting point for the enantioselective synthesis of natural products. For a good lead reference, see: Tun, M. K. M.; Herzon, S. B. *J. Org. Chem.* **2012**, *77*, 9422.
(20) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.
(21) Oare, D. A.; Heathcock, C. A. Stereochemistry of the Base-Promoted Michael Addition Reaction. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. *19*, pp 227−408.
(22) Kwan, E. E.; Sheerer, J. R.; Evans, D. A. *J. Org. Chem.* **2013**, *78*, 175.
(23) Xue, H.; Gopal, P.; Yang, J. *J. Org. Chem.* **2012**, *77*, 8933.
(24) Julia, S. A.; Eschenmoser, A.; Heusser, H.; Tarköy, N. *Helv. Chim. Acta* **1953**, *36*, 1885.
(25) Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1745.
(26) Dillen, J. L. M. *J. Org. Chem.* **1984**, *49*, 3800.
(27) No supporting experimental evidence was provided in ref 17 for the stereochemical assignment of **5**.
(28) Tricyclic intermediates **18** and **19** have two additional retro-Michael reactions available to them. C9−C10 and C11−C10 bond cleavage might occur; however, it is not possible to discern whether or not these processes are operative under these conditions.
(29) Prestwich, G. D.; Solheim, B. A.; Clardy, J.; Pilkiewicz, F. G.; Miura, I.; Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1977**, *99*, 8082.
(30) For select examples of tandem oxy-Cope/transannular carbonyl ene reactions, see: (a) Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925. (b) Anagnostaki, E. E.; Zografos, A. L. *Org. Lett.* **2013**, *15*, 152.
(31) Swaminathan, S. *J. Indian Chem. Soc.* **1984**, *61*, 99.
(32) Ravikumar, V. T.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron Lett.* **1985**, *26*, 6137.
(33) Shanmugam, P.; Devan, B.; Srinivasan, R.; Rajagopalan, K. *Tetrahedron* **1997**, *53*, 12637.