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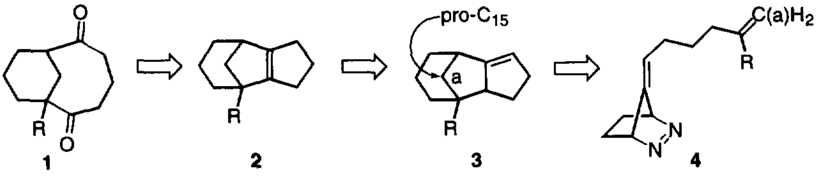
INTERMOLECULAR DIYL TRAPPING REACTIONS WITH ALLENE DIYLOPHILES

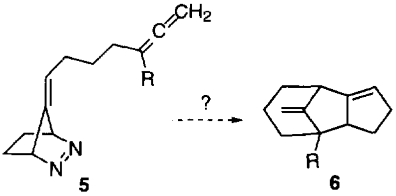
Xiaodong Lin & R. Daniel Little*

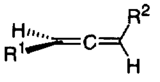
Department of Chemistry
University of California, Santa Barbara
Santa Barbara, CA 93106

ABSTRACT: Stereo- and regioselective intermolecular diyl trapping reactions were observed in these, the first examples of cycloaddition using allene diylophiles. Copyright © 1996 Elsevier Science Ltd

The intramolecular diyl trapping reaction provides an efficient route to the bridged ring system **3**.[1] We wish to exploit this discovery in the development of a new pathway to taxol analogs.[2] This requires the conversion of **3** to a tetrasubstituted tricyclic alkene **2**, and oxidative cleavage to afford **1**, a system possessing the A,B-portion of the ring system common to these materials. Our initial efforts have focused upon systems devoid of the C_{15} gem methyl group found in the naturally occurring materials. Whether the functionality is important *vis a vis* its influence on biological activity is unknown, as systems devoid of this unit have not been available for screening.[3] We have devised a plan to introduce them after the diyl trapping reaction. It calls for an intramolecular diyl trapping reaction (**5** → **6**), followed by cyclopropanation of the exocyclic alkene, and hydrogenolysis in a manner similar to that used by Trost and coworkers in conjunction with their taxol model studies.[4] Utilization of this strategy required the first exploration of allenes as diylophiles. Toward this end, we have examined the intermolecular cycloaddition chemistry of the diyl derived from diazene **10** and allenes **7**, **8**, and **9**.[1,5]



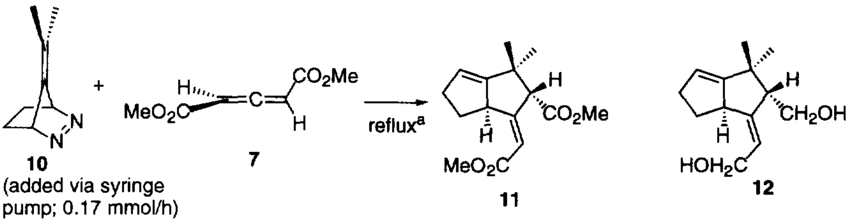




7, $R^1 = R^2 = CO_2CH_3$
8, $R^1 = H$, $R^2 = OCH_3$
9, $R^1 = CO_2CH_3$,
$R^2 = CH_2OCH_3$

Initial experiments were carried out using the symmetrical electron deficient allene diester **7**.[5a] In refluxing THF at an allene and diazene concentration of 1.2 and 0.4 M respectively, only a 15% yield of cycloadduct **11** was obtained.[6] Substantial amounts of oligomers were obtained (*vide supra*), an event that has *not* been a characteristic of diyl trapping chemistry. Interestingly, only one stereoisomer was produced. The stereochemistry was confirmed from a single crystal X-ray analysis of diol **12**, the solid derivative obtained by reduction of **11** with DIBAL (4 equiv, $PhCH_3$, -78 °C, 0.5 h).

Table 1



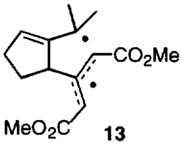
entry	[diazene], M[b]	[allene], M	solvent	yield **11** (%)
1	0.40	1.2	THF	15
2	$<2.6 \times 10^{-3}$	0.051	hexanes	70

a, 4.5 h total time. b, concentration estimated by using the total volume of diazene added per hour divided by the total volume of the reaction mixture.

As indicated in the table, a decrease in both the concentration of allene and diazene was accompanied by a dramatic increase in the yield of cycloadduct **11** and a substantial decrease in oligomer formation. The best yield, 70%, was obtained when a *ca.* 2.5 mM solution of the diazene was added slowly to a 51 mM solution of allene in refluxing hexanes; similar results were obtained in THF, though the yield was slightly less (64%).

Oxygen quenching studies once again proved effective in determining the diradical spin state associated with the cycloaddition.[7] Thus, when the experiment was conducted in the presence of a steady stream of oxygen, cycloadduct **11** was *not* produced. Given the very short lifetime of the singlet diyl and the fact that the concentration of oxygen in refluxing solvent is too low to allow reaction with the singlet,[7] we conclude that under the conditions that afford the optimal yield, **11** arises *via* interception of the triplet diradical.

While the direct competition of equal quantities of allene **7** and methyl acrylate for diyl revealed the diylophiles to be of comparable reactivity, the chemistry of **7** differs considerably from that of its simpler counterpart.[8] Oligomerization, for example, has not been reported for non-allenic diylophiles, yet it is the dominant pathway in the chemistry of allene **7** at 1.2 M. While the precise nature of the oligomers has not been defined, it is clear from the ^1H NMR spectrum that they consist of units made up of both diyl and allenic components. The oligomers arise *via* a stepwise process, presumably involving diyl **13**. A comparison of intermediates derived from each diylophile, *viz.* **13** and **14**, reveals added delocalization for the allene derived species. This may be reflected in a longer lifetime and a greater opportunity to be intercepted by the diylophile, ultimately leading to oligomer.



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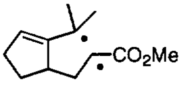

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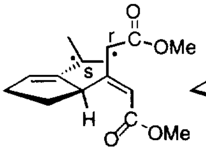
To rationalize the stereochemical outcome, we suggest that diradical **13** preferentially adopts a geometry wherein the plane of the five membered ring and the five-carbon side chain are nearly perpendicular. Of the geometries available, that portrayed in structure **15** minimizes ester-ester and ester-ring interactions relative to the alternatives formulations **16-18**. Sigma-bond formation between carbons C_r and C_s leads to the observed adduct, **11**.



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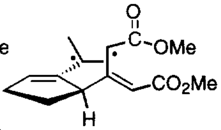

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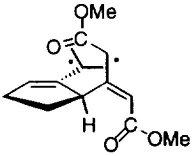

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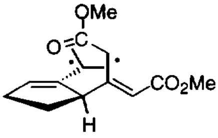

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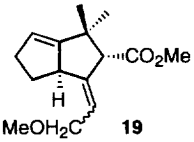
Finally, we have explored the chemistry of allenes **8** and **9**.[5b,c] The former, being electron rich at one end of the π-system, and neutral at the other, might be expected to intercept the diyl at the neutral π-bond. Cycloaddition failed to occur. Under the optimal reaction conditions described above (*viz.*, entry 2 of Table 1), allene **9** did, however, intercept the diyl to afford a 50% yield of **19** as a mixture of stereoisomers. No regioisomers were detected, cycloaddition preferentially occurring at the electron deficient end of the diylophile.



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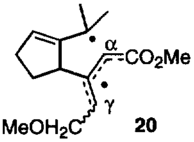
The regiochemical outcome is of interest. We suggest that its origin might simply be in the difference in the size of the coefficients at the potential reacting sites, C_α and C_γ in the SOMO of diradical **20**. The former being larger, should, and does correspond to the preferred reaction site. Such selectivity is reminiscent of the kinetic α-selectivity observed in alkylation of extended enolates.[9]



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In summary, we have explored the first examples of the diyl trapping reaction using allene diylophiles. While the details differ from that of their simpler olefinic counterparts, cycloaddition *is* possible and has been achieved in good yield. We are hopeful that an intramolecular variant will be at least as successful and will prove useful within the context of our ongoing efforts toward the synthesis of taxol analogs.

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6. NMR data for **11**: ^{1}H NMR 5.78 (t, 1H, J = 2.75), 5.44 (br s, 1H), 4.08 (m, 1H), 3.72 (s, 3H, non-conjugated CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 3.38 (t, J = 2.65, 1H), 2.74 (m, 1H), 2.51 (m, 1H), 2.31 (m, 1H), 1.49 (m, 1H), 1.31 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR 171.3 (non-conjugated CO), 166.3 (CO, conjugated), 162.6, 156.7, 119.6, 116.4, 64.5, 52.6, 51.7 (CO_2CH_3), 51.0 (CO_2CH_3), 41.5, 34.5, 34.1, 24.7 (CH_3), 22.2 (CH_3). High resolution ms: 264.1356 (calc. mass 264.1362).
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