# Higher-order cycloaddition reactions in natural product synthesis

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<u>Abstract:</u> Metal-template has been effectively utilized to obviate the problems encountered in higher-order cycloaddition reactions. Highly functionalized bicyclic systems can be assembled using this methodology and as many as five contiguous stereogenic centers can be readily accessed. This technology has been used to prepare the frameworks of naturally occurring anatoxin *a* and cerorubenol.

Higher-order cycloaddition reactions (1), e.g. $6\pi+4\pi$, $4\pi+4\pi$ and $6\pi+2\pi$ combinations, proceed with high levels of diastereoselectivity. The reactions of these extended π-arrays, however, are usually not well-behaved and the lack of *peri*-selectivity often translates into poor chemical efficiency. Employing a transition-metal template, that would precomplex with the reacting partners, is an appealing idea. The process would then be rendered temporarily intramolecular and follow a more efficient pathway (eq 1) (2).
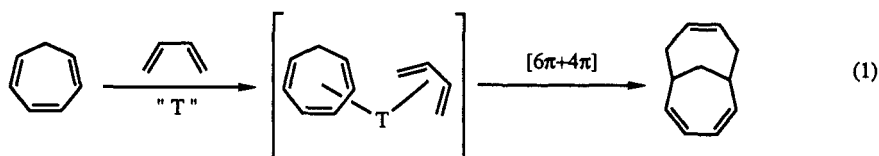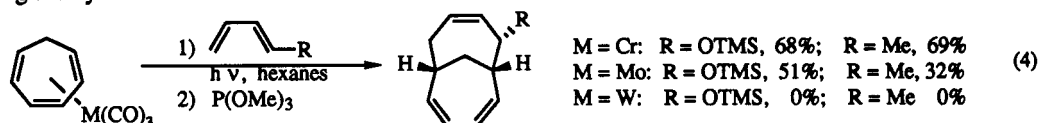

Initial studies that focused on the behavior of the parent cycloheptatriene chromium complex with electron-rich dienes in a photochemical environment led to the formation of [6+4] cycloadducts. In each case, only one product was formed that displayed *endo*-stereochemistry (eq 2). The dramatic scope
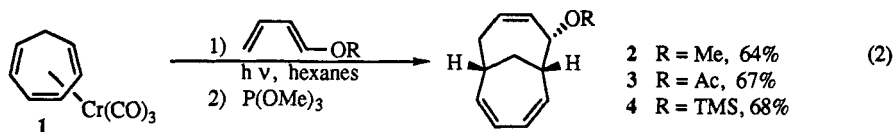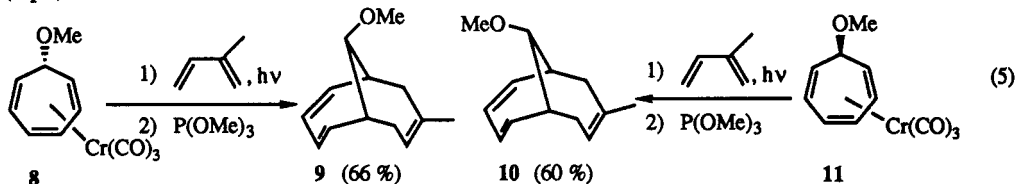

of this methodology was illustrated by attenuating the electronics of the 4π addend. Thus **1** gives [6+4] adducts upon reaction with the very electron-rich diacetoxybutadiene, a hydrocarbon diene as well as the very electron-deficient dimethyl muconate (eq 3). These reactions, therefore, override the electronic constraints that normal cycloadditions are subject to (3).
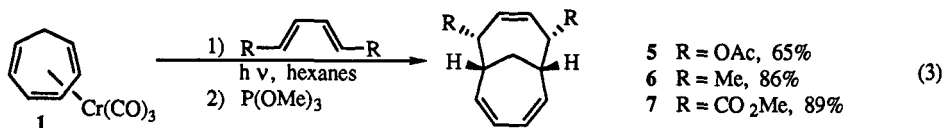
A comparative study was also undertaken to probe the efficacy of employing the other members of the group VI triad, *viz.* Mo and W and we observed that whereas Cr presented the most efficient means of bringing about this transformation, Mo was less effective and, to date, W has not yielded any desirable results (eq 4). Whereas Mo seems to be too labile, W appears to be too robust for the purposes of accessing the cycloadditive route.

$$M = Cr: \quad R = OTMS, \; 68\%; \quad R = Me, \; 69\%$$
$$M = Mo: \quad R = OTMS, \; 51\%; \quad R = Me, \; 32\% \qquad (4)$$
$$M = W: \quad R = OTMS, \; 0\%; \quad R = Me \;\; 0\%$$

To explore the feasibility of transferring relative stereochemistry from the 7-position of cycloheptatriene to the product, both the 7-*endo*-methoxy complex **8** and the 7-*exo*-**11** were treated with isoprene. In each case only one product was obtained, showing clearly that the stereochemical outcome on the bridging carbon of the cycloadduct can be controlled by judicious choice of the starting metal complex (eq 5).

A reaction that serves to further broaden the scope of this methodology is illustrated in eq 6. Thus, treatment of the 7-substituted **12** with methyl sorbate provided cycloadduct **13** demonstrating the creation of *five contiguous stereogenic centers*, with predictable stereocontrol, in one step.
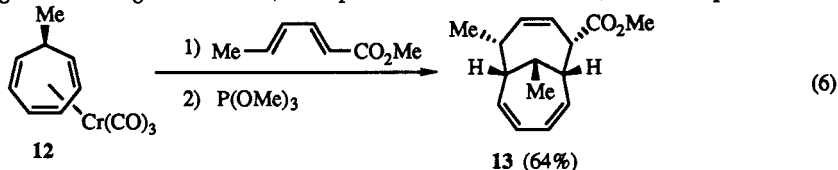

Since the well-established thermal [6+4] cycloadditions of tropone proceed via the *exo*-transition state (4), it was relevant to probe the possibility of accessing the *endo*-[6+4]-cycloadducts of tropone. Thus the ketal complex **14** was allowed to cycloadd to pipyrelene. Cycloaddition, followed by sequential decomplexation and hydrolysis of the ketal led to the keto product **15**. The *endo* [6+4] adducts of tropone are now within reach. For comparison purposes, an authentic sample of the known *exo*-adduct was also prepared. These experiments demonstrated the stereocomplementarity of the two processes (eq 7).
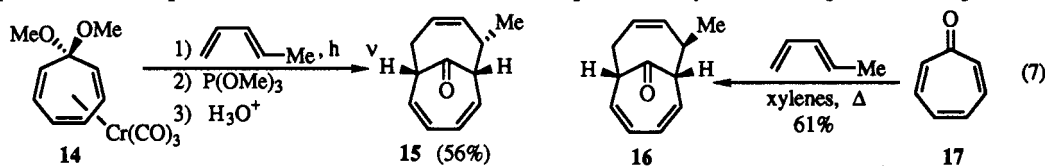
When the [6+4] cycloaddition reaction employing transition-metal templates had been firmly established, the metal-mediated [6+2] reaction emerged as a natural extension of this methodology. The profound observation that irradiating the reaction mixture consisting of complex **1** and an acrylate results in the formation of a 1:1 adduct has opened up an efficient avenue for accessing the bicyclo[4.2.1]nonane framework (5).

One of the natural products that was targeted for the application of this methodology was anatoxin *a*, isolated initially from the blue-green algae. The powerful neuromuscular polarizing property of

anatoxin *a* (6) has stimulated vigorous synthetic activity and several preparations of this compound and its analogues have been reported in the literature (7). Our retrosynthetic analysis suggested that anatoxin *a* could be obtained from the [6+2] cycloadduct of an appropriately substituted azepine (eq 8). For the

Anatoxin a   **18**   **19 (92%)**
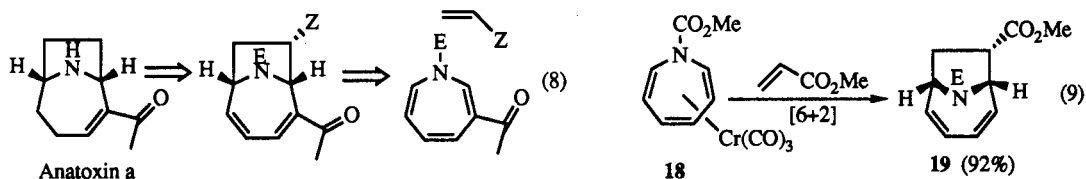
purpose of establishing a viable higher-order cycloaddition route to this natural product, azepine complex **18** was treated with methyl acrylate to provide adduct **19** (eq 9). This constitutes an extremely efficient synthesis of the framework of homotropane alkaloids.

Also noteworthy are the efficient [6+4] cycloaddition reactions of complex **18** with both electron-deficient and electron-rich dienes (eq 10). The structure of cycloadduct **23** was further confirmed by X-ray crystallography, which not only established the [4.4.1]undecane structure but also the *endo*-stereochemical disposition of the product.

	R^1	R^2	R^3	Yield
20	H	H	OAc	75%
21	H	H	OTMS	79%
22	H	OTMS	H	87%
23	Me	H	CO_2Me	83%

$E = CO_2Me$ (10)
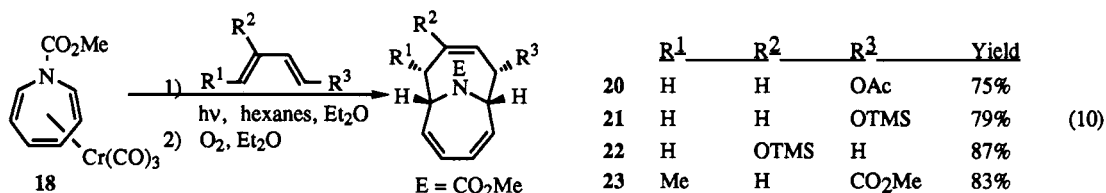
Another appealing application of these reactions would be the cycloadditive entry into the eight-membered rings, which are prevalent in several natural products. Thus the [6+2] cycloadducts of heterocyclic trienes would be prepared and a simple excision of the heteroatom would then lead to the formation of cyclooctanoids and the stereochemical information created during the cycloaddition step would be transferred to the final products (eq 11).
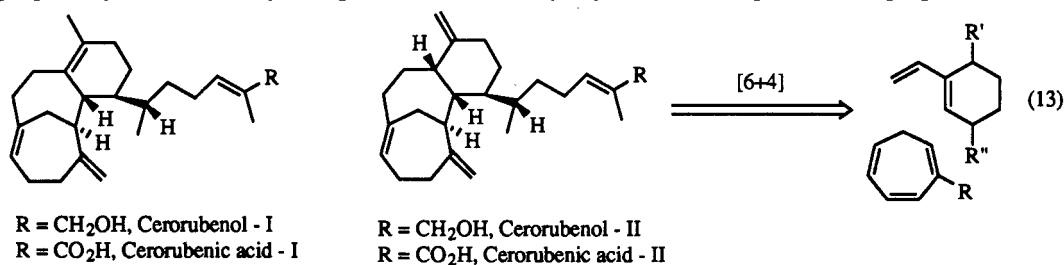

(11)
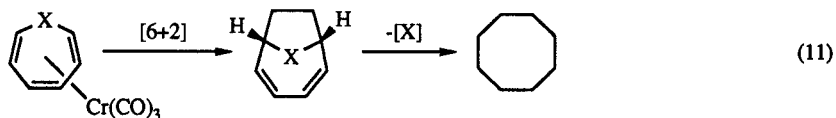
To access the eight-membered rings adduct **24** was first hydrogenated and then treated with LiAlH$_4$ to provide the amino-alcohol **25** which was first treated with MeI and then with moist Ag$_2$O and pyrolyzed in the presence of KOH. This Hofman elimination sequence provided a 1:1 mixture of the isomeric cyclooctenes **26** and **27** in good yield (eq 12) (8).


24   **25**   **26**   **27**
$E = CO_2Me$
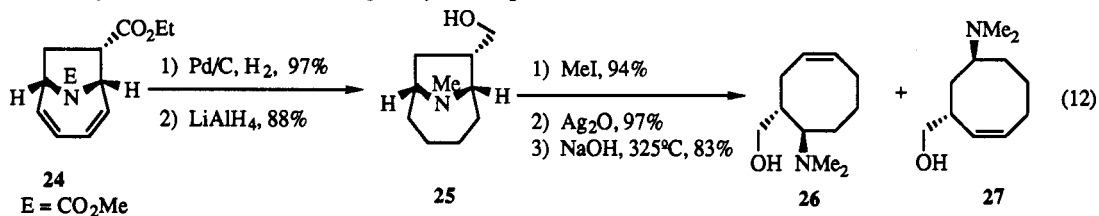
Another arena of natural products where this technology seems to have an attractive application is the cerorubenate sesterterpenes, isolated from *C. rubens* (9) Our retrosynthetic analysis suggested that the tricyclic framework of these sesterterpenes could be readily accessed via a [6+4] combination of an

appropriately substituted cycloheptatriene and a vinyl cyclohexene (eq 13). The preparation of the

R = CH$_2$OH, Cerorubenol - I
R = CO$_2$H, Cerorubenic acid - I

R = CH$_2$OH, Cerorubenol - II
R = CO$_2$H, Cerorubenic acid - II

requisite diene commenced with the commercially available epimeric mixture of (+)-dihydrocarvone, **28**. Separation of the diastereomers provided the optically pure compound, which was converted into the kinetic enolate and then treated with PhNTf$_2$. Treatment of the resultant triflate with tributylvinyl tin in the presence of catalytic amounts of Pd(0) provided the 4π addend **30**, which reacted with **1** to afford the tricyclic framework of cerorubenates in optically active form. This reaction was highly diastereoselective and the formation of only one product was observed. Also note that of the three contiguous stereogenic centers found in the natural products, two have the correct absolute configuration.
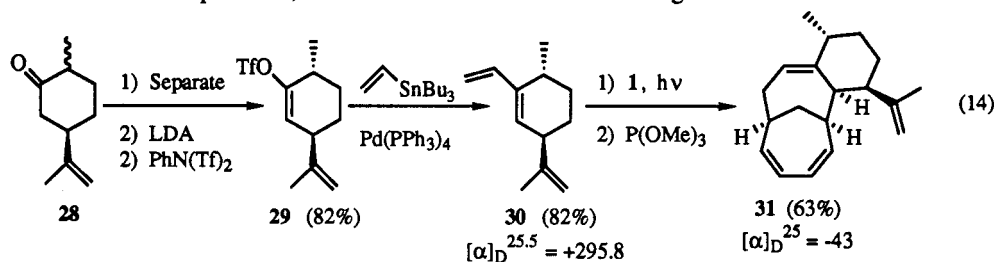
28   **29** (82%)   **30** (82%)   **31** (63%)
                                      $[\alpha]_D^{25.5} = +295.8$ $[\alpha]_D^{25} = -43$

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