J. Org. Chem. 1991, 56, 561–567

Materials. The (*E*)-cinnamamides were prepared from the cinnamic acids (Aldrich) via reaction of the acid chlorides with ammonia, methylamine, or dimethylamine and purified by recrystallization from hexane or chloroform or, for the noncrystalline *E*-4–6, silica gel chromatography. GC analysis indicated that all of the (*E*)-cinnamamides used in spectroscopic and photochemical studies were of >99% purity. Irradiation of the (*E*)-cinnamamides with the Pyrex-filtered output of a Hanovia 450-W high-pressure mercury arc provided isomer mixtures containing 50–75% *Z* isomer. Silica gel chromatography using chloroform eluant provided samples of the (*Z*)-cinnamamides containing <5% *E* impurity. In most cases, repeated chromatography provided samples containing <1% *E* impurity and these purified samples were used except as indicated in the footnotes to Table V. Both the *E* and *Z* isomers were fully characterized by means of their ^{1}H NMR and IR spectra and high-resolution mass spectroscopy.

Spectrophotometric grade dichloromethane (Aldrich) was refluxed over calcium hydride and freshly distilled prior to use in photochemical studies. Other solvents were spectral grade and used as received. BF_3–OEt_2 (Aldrich) was used as received until discolored and then distilled prior to use.

Acknowledgment. This work is supported by the National Science Foundation (CHE 8922835).

Supplementary Material Available: ^{1}H NMR, HRMS, and melting point data for solid compounds and ^{1}H NMR spectra of the (*E*)- and (*Z*)-cinnamamides and their BF_3 complexes (30 pages). Ordering information is given on any current masthead page.

Stereochemistry of [2 + 2] Photocycloaddition of Cyclic Enones to Alkenes: Structural and Mechanistic Considerations in Formation of Trans-Fused Cycloadducts

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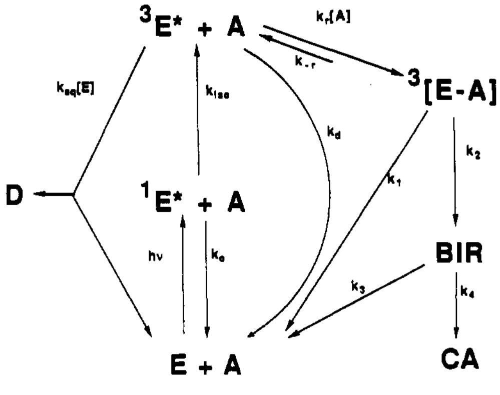
Photocycloaddition of 2-cyclohexenone to cyclopentene gives four [2 + 2] adducts, rather than only two as reported previously. Differentiation between the cis–anti–cis and cis–syn–cis structures was made on the basis of differences in ^{13}C chemical shifts in the two isomers. The structures of the two trans-fused adducts, which were not isolated, derive from their base-catalyzed epimerization to the corresponding cis-fused isomers. One trans-fused and one cis-fused cycloadduct are formed initially in a ratio of 2:1, respectively, upon photoaddition of testosterone acetate to cyclopentene, but this ratio changes in favor of the cis-fused isomer as the irradiation progresses due to secondary reactions. These adducts were identified by X-ray crystallography as the trans-fused (4α,5β) and cis-fused (4α,5α) structures. Epimerization of the trans-fused adduct in base led to isolation of the alternative cis-fused adduct (4β,5β) whose X-ray crystal structure was also determined. The X-ray structure of the oxime of the trans-fused photoadduct of 2-cyclohexenone and tetramethylethylene was also obtained for structural comparison with the steroid enone adducts. These are believed to be the first definitive structure determinations of trans-fused bicyclo[4.2.0]octan-2-ones. The assignments of ^{1}H NMR coupling constants to vicinal cis and trans protons on the cyclobutane ring are based on the relevant dihedral angles obtained from the X-ray structures and from molecular modeling. Mechanisms for the formation of trans-fused adducts from both planar and twisted cyclohexenone triplets are discussed.

The [2 + 2] photocycloaddition of cyclic enones to alkenes is arguably the most useful photochemical reaction to synthetic organic chemists, as a route to annelated products or products of subsequent cyclobutane fragmentation.[1] The synthetic utility of this reaction was first vividly demonstrated by Corey in his synthesis of the terpenoid caryophyllene, in which the natural product featuring trans fusion of a four- and nine-membered ring is produced by elaboration of a trans-fused adduct formed upon [2 + 2] photocycloaddition of cyclohexenone to isobutylene.[2] The mechanism generally used[1] to describe this reaction, formulated first by Corey[3] and later elaborated by de Mayo, is shown in Scheme I.[4] According to this mechanism, the lowest triplet state of the enone (initially thought[3] to be an n,π* triplet but now known to be a π,π* triplet)[5] reacts with the alkene to give an oriented π-complex or triplet exciplex, which then collapses to a triplet

Scheme I. The Corey–de Mayo Mechanism



E = enone, A = alkene, D = enone dimer, BIR = 1,4-biradical, CA = cycloadduct

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[1] Baldwin, S. W. *Org. Photochem.* 1981, *5*, 123. Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984; pp 61–144. Carless, H. A. J. In *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Royal Society of Chemistry: London, 1986; pp 95–117. Wender, P. A. In *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; Royal Society of Chemistry: London, 1986; pp 163–188.

[2] Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* 1964, *86*, 485.

[3] Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* 1964, *86*, 5570.

[4] (a) De Mayo, P. *Acc. Chem. Res.* 1971, *4*, 41. (b) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* 1977, *99*, 3559.

[5] (a) Schuster, D. I.; Heibel, G. E.; Brown, P. B.; Turro, N. J.; Kumar, C. V. *J. Am. Chem. Soc.* 1988, *110*, 8261. (b) For a recent review of enone photochemistry, see: Schuster, D. I. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons, Ltd: Chichester, U.K., 1989; pp 623–756.

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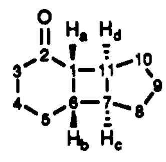
1,4-biradical. After a spin–flip, the rate of which is slower than rotation around C–C single bonds, cyclization occurs competitive with fragmentation. Although Loutfy and de Mayo[4] concluded that exciplex formation from the enone triplet is essentially irreversible, they suggested that reversion to ground-state starting materials from all of the reaction intermediates is, at least in principle, competitive with progress to the next reaction stage.

Although recent studies by Schuster and co-workers[5] cast serious doubt on the role of exciplexes in these photochemical cycloadditions, this is not especially relevant to the present report. Rather, we wish to concentrate on the formation of trans-fused cycloadducts of cyclohexenones and alkenes, and its relationship to the structure of the reaction intermediates, particularly the enone triplet excited state.

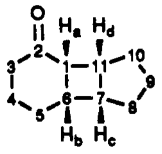
Corey and co-workers[2,3] first demonstrated that the major isomer on photoaddition of simple cyclohexenones to alkenes is frequently the trans-fused [2 + 2] cycloadduct. This finding has been confirmed repeatedly.[1] Corey suggested that trans-fused bicyclo[4.2.0]octan-2-ones could be formed from a "a metastable form of the enone with trans-oriented out-of-plane hydrogens".[3] This explanation is consistent with later calculations of Devaquet[6] which showed that the T_1 (π,π^*) state of acrolein, a model α,β-unsaturated ketone, undergoes energetic relaxation by twisting around the C=C bond. Schuster and co-workers[7,8] reported that, for 4,4-dimethylcyclohexenone, photocycloaddition to alkenes is competitive with the lumiketone rearrangement, in which substantial twisting is required in order to form the bicyclo[3.1.0]hexan-2-one ring system. Quenching studies established that in this system photorearrangement and photoadditions arise from a common triplet state, concluded to be a twisted π,π^* triplet state, or less likely from two thermally equilibrated triplets.[7,8] Nanosecond flash photolysis studies have provided strong evidence for the formation of twisted π,π^* triplets on photoexcitation of cyclic enones.[9-11]

It therefore seemed reasonable to suggest[5b,7] that cyclic enone triplets which are conformationally flexible with respect to twisting around the C=C bond interact with alkenes to give a highly twisted 1,4-biradical intermediate (whether or not via a prior exciplex) which can close to trans-fused cycloadducts competitive with relaxation to an unstrained biradical which affords cis-fused cycloadducts. However, it was reported by Rubin[12] and Lenz[13] that trans-fused cycloadducts are preferentially formed even from steroid enones such as testosterone propionate in which the lowest energy π,π^* triplet state is essentially planar, according to low temperature spectroscopy[14] and time-resolved photoacoustic calorimetry at room temperature.[15] The present study was undertaken in order to attempt to resolve this mechanistic dilemma, and to obtain structural data on trans-fused cycloadducts using both NMR spectroscopy and X-ray crystallography.

Table I. ^{13}C NMR and ^{1}H NMR Parameters for Isomers 1 and 2



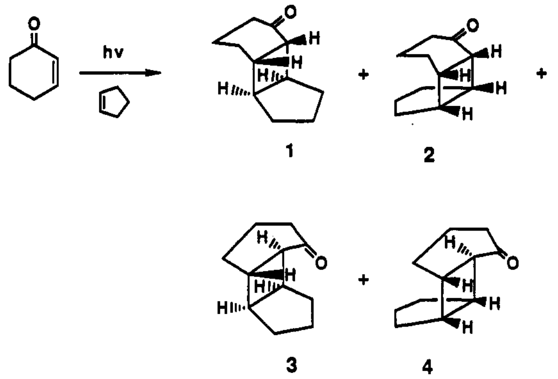
1



2

resonance assignments	^{13}C ppm 1	^{13}C ppm 2	^{1}H ppm 1	^{1}H ppm 2	J_{HH}, Hz
C1	47.9	44.3	2.7 q	3.2 m	J_{ab} 12.1
C2	215.3	215.0			J_{ad} 6.6
C3	37.4	38.2			
C4	19.9	20.6			
C5	24.8	23.7			
C6	42.0	43.0	2.5 m	3.0 m	
C7	40.6	40.0	2.2 m	2.8 m	
C8	33.1	28.9			
C9	27.9	27.5			
C10	32.5	29.1			
C11	41.9	42.3	2.4 m	3.0 m	

Scheme II



Results

Photocycloaddition of 2-Cyclohexenone to Cyclopentene. Corey[3] reported that photoaddition of 2-cyclohexenone (CH) to cyclopentene (CP) in pentane at low temperature (dry ice bath) gave two stereoisomeric bicyclo[4.2.0]octan-2-ones, differing only in the geometry (cis or trans) of the 6–4 ring fusion; the 4–5 ring fusion was assumed to be cis.[16] In the present study, irradiation of a mixture of CH and CP in acetonitrile at room temperature led to four adducts A–D according to GC and GC/MS analysis, in yields of 68%, 7%, 25%, and <1%, respectively. Upon extended treatment of the mixture of the adducts with base, the adducts B and C (presumably trans-fused isomers)[3] disappeared while the amounts of adducts A and D (presumably the two cis-fused isomers) increased. The ratio of adducts A and D, both of which had carbonyl IR bands at 1710 cm^{-1} characteristic of cis-fused adducts,[3] was 3:1. They were separated by HPLC, and their structures were determined spectroscopically.

The assignment of stereochemistry to the cis-fused isomers A and D was based most unequivocally on the differences in the ^{13}C chemical shifts of C-1, C-8, and C-10 in the two isomers (see Table I). These occur at 47.9, 33.1, and 32.5 ppm in the case of A and 44.0, 28.9, and 29.1 ppm

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(6) Devaquet, A. *J. Am. Chem. Soc.* **1972**, *94*, 5160.

(7) Schuster, D. I.; Greenberg, M. M.; Nuñez, I. M.; Tucker, P. C. *J. Org. Chem.* **1983**, *48*, 2615.

(8) Schuster, D. I.; Brown, P. B.; Capponi, L. J.; Rhodes, C. A.; Scaiano, J. C.; Tucker, P. C.; Weir, D. *J. Am. Chem. Soc.* **1987**, *109*, 2533.

(9) Bonneau, R. *J. Am. Chem. Soc.* **1980**, *102*, 3816.

(10) Schuster, D. I.; Dunn, D. A.; Heibel, G. E.; Rao, J. M.; Brown, P. B.; Bonneau, R. *J. Am. Chem. Soc.* Submitted for publication.

(11) Heibel, G. E. Ph.D. Dissertation, New York University, 1990.

(12) Rubin, M. B.; Maymon, T.; Glover, T. *Isr. J. Chem.* **1970**, *8*, 717.

(13) Lenz, G. R. *Rev. Chem. Intermed.* **1981**, *4*, 369. Lenz, G. R. *J. Chem. Soc., Chem. Commun.* **1982**, 803.

(14) Marsh, G.; Kearns, D. R.; Schaffner, K. *J. Am. Chem. Soc.* **1971**, *93*, 3129. Jones, C. R.; Kearns, D. R.; Wing, R. M. *J. Chem. Phys.* **1973**, *58*, 1370. Jones, C. R.; Kearns, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 344.

(15) Schuster, D. I.; Heibel, G. E.; Caldwell, R. A.; Tang, W. *Photochem. Photobiol.* **1990**, *52*, 645.

(16) While at least one case of trans fusion of four- and five-membered rings is known [Scharf, D. H. *Tetrahedron Lett.* **1967**, 4231], no examples of photocycloadditions of cyclic enones to give trans-5–4 ring junctions have been reported, to our knowledge.

in the case of D, respectively. Steric crowding around C-1, the bridgehead carbon α to the carbonyl, and severe van der Waals interactions between the six-membered ring and C-8 and C-10 in the cis-syn-cis adduct should result in shielding of these carbons relative to the same carbons in the cis-anti-cis adduct where there is no such interaction.[17,18] Thus, adduct A is assigned structure **1** and D structure **2** (see Scheme II). This assignment is consistent with the general finding that yields of cis-anti-cis cycloadducts are generally much higher than those of the corresponding cis-syn-cis isomers.[1,19,20]

These assignments are consistent with the ^1H NMR spectra of A and D. The 300-MHz ^1H NMR spectrum of A is very complicated, but peak assignments could be made based on decoupling and 2D-COSY experiments. The chemical shifts and coupling constants for the critical protons H_a–H_d (see structure **1**) are also given in Table I. The resonance (doublet of doublets) at 2.7 ppm is assigned to H_a, which is expected to be most deshielded due to the adjacent carbonyl group and the ring strain. Stereochemical assignments in cyclobutanes are notoriously difficult based upon ^1H NMR data; because of the sensitive dependence of vicinal proton coupling constants on the dihedral angle, either cis or trans coupling may be larger in cyclobutanes depending on the exact conformation of the four-membered ring (see Discussion). The H–C–C–H dihedral angles were therefore determined for **1** using molecular mechanics calculations (MACROMODEL),[21] and are −122° for H_a–C–C–H_d and −10.4° for H_a–C–C–H_b. Based on the Karplus relationship[22] the smaller coupling constant of 6.6 Hz is assigned to trans coupling of H_a to H_d while the larger coupling constant of 12.1 Hz is assigned to cis coupling with H_b.[23,24] The ^1H NMR resonances of isomer D, assigned structure **2**, occurred further downfield than those of **1**, consistent with steric crowding in this molecule. The assignments to H_a–H_d were again made on the basis of decoupling and 2D-COSY studies (Table I), although the resonances were less well resolved than in the case of **1**. For **2**, the low-field resonance for H_a shows coupling to adjacent protons (H_b and H_d) of 4.5 and 6.6 Hz, respectively. Based upon the calculated dihedral angles (see above) of 2.2° and 3.0°, respectively, both coupling constants were expected to be significantly larger than observed (9–10 Hz). The other two isomers in the original product mixture could not be obtained in pure form, but from the isomerization experiments they are assigned the trans-anti-cis (B) and trans-syn-cis (C) structure **3** and **4**, respectively. It would be of interest to have the ^{13}C and ^1H NMR spectra of **3** and **4** for comparison with those of their cis-fused isomers and related compounds in the literature.

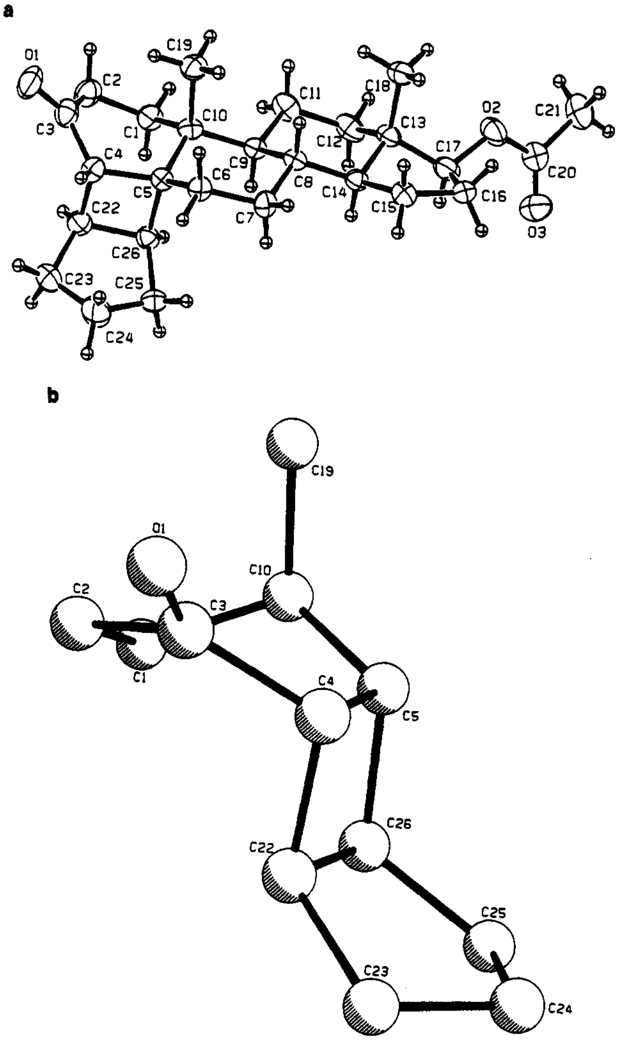
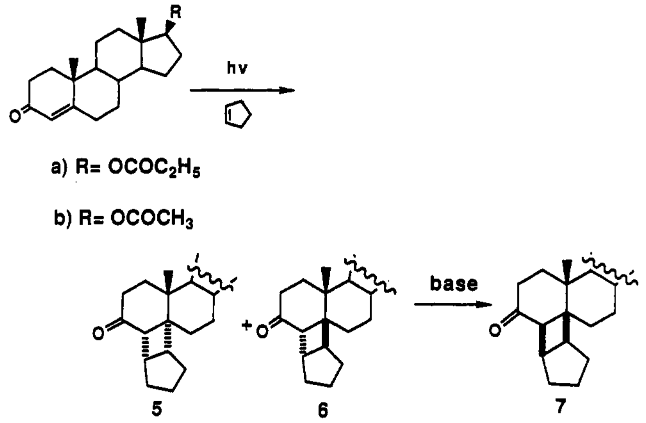


Figure 1. (a) ORTEP diagram of the structure of **5b** showing the atom labeling scheme and 30% probability thermal ellipsoids. (b) Close-up view of the fusion of the cyclobutane and cyclohexanone rings.

Scheme III



Photocycloaddition of Testosterone Acetate to Cyclopentene. Photocycloaddition of testosterone propionate to cyclopentene (CP) was reported by Rubin[12] to give two major products assigned structures **5a** and **6a** on the basis of NMR and IR data and base isomerization experiments. The major product was concluded to be the cis-fused adduct **5a**, but the adduct ratio was reported by Rubin to change as a function of solvent, temperature, and

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[17] Williams, J. R.; Lin, C.; Chodash, D. F. *J. Org. Chem.* **1985**, *50*, 5815. Lange, G. L.; Decicco, C. P.; Willson, J.; Strickland, L. *Ibid.* **1989**, *54*, 1805.

[18] Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy. High-Resolution Methods and Applications in Organic Chemistry and Biochemistry*; VCH Verlagsgesellschaft: Weinheim, FRG, 1987; p 115ff.

[19] Eaton, P. E. *J. Am. Chem. Soc.* **1962**, *81*, 2344.

[20] Lam, E. Y. Y.; Valentine, D.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 3482.

[21] Lipton, M.; Still, W. C. *J. Comp. Chem.* **1988**, *9*, 343. Still, W. C. Macromodel; Columbia Univ., 1986.

[22] Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11; Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; John Wiley: New York, 1981; p 208 ff.

[23] (a) Rinaldi, P. L.; Salomon, R. G. *J. Org. Chem.* **1983**, *48*, 3182. (b) Bourhis, M.; Goursolle, M.; Leger, J.-M.; Duboudin, J. G. *Tetrahedron Lett.* **1989**, *30*, 4665. (c) Lewis, F. D.; Baranyck, S. V. *J. Am. Chem. Soc.* **1989**, *111*, 8653.

[24] A referee carried out MM calculations on **1** and obtained corresponding dihedral angles of −160° and +34°, respectively, based upon which values of $J_{ad} = 11.6$ Hz and $J_{ab} = 7.7$ Hz were predicted, directly opposite to the assignments made by us. This in itself illustrates the risky nature of assignments of cyclobutane stereochemistry based purely on ^1H NMR data.

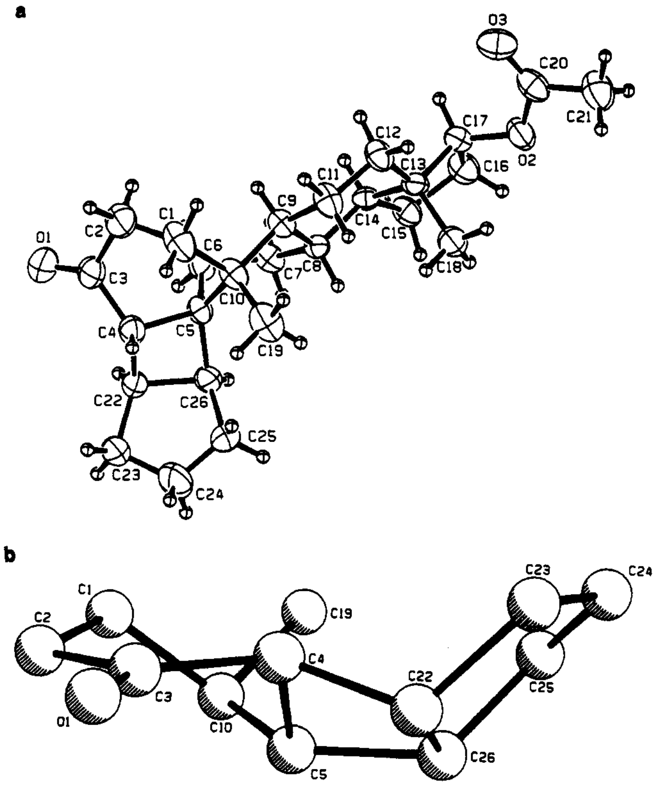


Figure 2. (a) ORTEP diagram of the structure of **6b** showing the atom labeling scheme and 30% probability thermal ellipsoids. (b) Close-up view of the fusion of the cyclobutane and cyclohexanone rings.

olefin concentration.[12,25] Since no X-ray structures of analogous trans-fused enone–alkene adducts have been reported, we decided to prepare stereoisomeric adducts of testosterone acetate and cyclopentene and to determine their structures unequivocally using X-ray crystallography.

Following Rubin's procedure[12] for testosterone propionate, the corresponding acetate was irradiated in neat cyclopentene with a 450-W lamp for 7 h in a water bath. Two products in a ratio of close to 1:1 were detected by capillary GC, and these could be separated by chromatography on Florisil. Recrystallization from methanol and hexane, respectively, gave crystals suitable for X-ray analysis. From the X-ray structures of the two cycloadducts shown in Figures 1 and 2, it is clear that they are the cis-fused $4\alpha,5\alpha$ and trans-fused $4\alpha,5\beta$ adducts **5b** and **6b**, respectively (see Scheme III). Upon extended treatment of **6b** with alcoholic KOH, an alcoholic product was formed, which after reacetylation with acetic anhydride in pyridine gave a crystalline material whose structure was shown by X-ray crystallography (Figure 3) to be the cis-fused $4\beta,5\beta$ adduct **7b**. Thus, the adduct structures originally assigned on the basis of spectroscopic data by Rubin[12] are confirmed. To our knowledge, the X-ray structure of **6b** is the first reported for a trans-fused cycloadduct of a cyclohexenone and an alkene. Thus, the structural features of these stereoisomeric cycloadducts can be directly analyzed (see Discussion).

Attempts to repeat Rubin's finding[12] that the adduct ratio in the propionate analogue depended on reaction conditions led to the discovery that the ratio of **5b** to **6b** was strongly dependent on the time of irradiation. At low conversions of starting enone, the trans-fused adduct **6b** is favored by a factor of 2:1; as the irradiation continues the ratio gradually shifts in favor of the cis-fused isomer **5b**, eventually reaching a ratio of **5b**:**6b** of ca. 4:1, as reported in Rubin's study. Further studies have demonstrated that both **5b** and **6b** are undergoing secondary photoreactions, to be reported separately, in which **6b** is consumed more efficiently.[26,27]

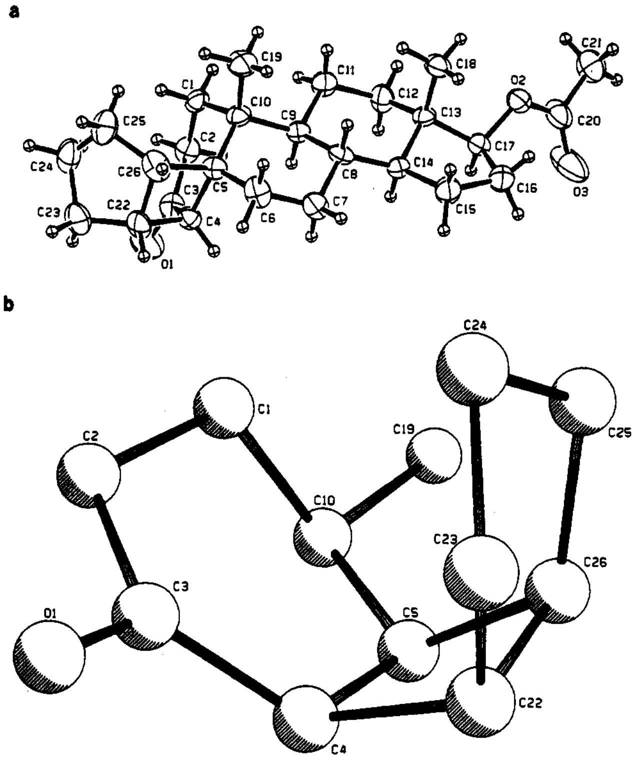
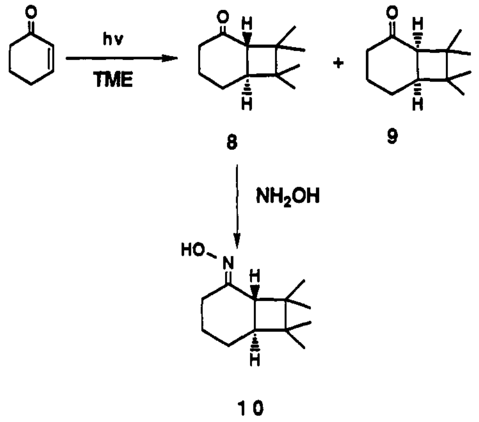


Figure 3. (a) ORTEP diagram of the structure of **7b** showing the atom labeling scheme and 30% probability thermal ellipsoids. (b) Close-up view of the fusion of the cyclobutane and cyclohexanone rings.

Scheme IV



Photocycloaddition of 2-Cyclohexenone to Tetramethylethylene (TME). The photochemical addition of 4,4-dimethyl-2-cyclohexenone (DMCH) to TME was first investigated by Chapman et al.,[28] who found that the trans-fused adduct was the main product. In order to acquire structural information about trans-fused adducts of conformationally flexible cyclohexenones vis a vis adducts of conformationally rigid enones, such as testosterone acetate, the photoaddition of 2-cyclohexenone to TME in

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[25] De Mayo, P.; Loutfy, R. O.; Rubin, M. B., unpublished results quoted in footnote 6b in ref 4a.

[26] Schuster, D. I.; Kaprinidis, N., unpublished results.

[27] Secondary photoreactions of structurally analogous photoadducts have been reported by Lenz, G. R. *Tetrahedron* **1972**, *28*, 2195.

[28] Chapman, O. L.; Ostren, D.; Lassila, J.; Nelson, P. *J. Org. Chem.* **1969**, *34*, 811.

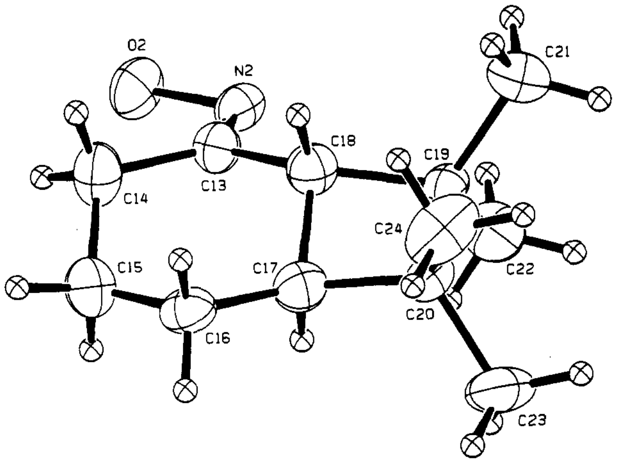

Figure 4. ORTEP diagram of one of the two independent molecules in the structure of **10**. Atom labeling scheme and 30% probability ellipsoids are depicted.

acetonitrile was reinvestigated. The reaction resulted in the formation of two [2 + 2] cycloadducts **8** and **9** in the ratio 4:1 (see Scheme IV). No oxetane is formed under these conditions.[28] On the basis of base isomerization studies, the trans-fused adduct **8** appeared to be the major product, as previously reported for DMCH.[28]

The mixture of isomers was converted into oxime derivatives, fractional crystallization of which led to the isolation of crystals of the oxime of the trans-fused adduct, **10**. The X-ray structure of this compound is shown in Figure 4. The bridgehead hydrogens in **10** are clearly trans, as assigned[28] to the major photocycloadduct in the case of DMCH and TME based upon spectroscopic and chemical data. The NMR coupling constant between the bridgehead protons in **8** is 12.9 Hz, a value consistent with the dihedral angle of 170° found in the X-ray structure. This finding demonstrates that in appropriately constrained cyclobutanes, coupling of vicinal trans protons is not necessarily small (0–3 Hz), as has been sometimes claimed in the literature.[23b,29]

Discussion

The stereochemistry associated with the photoaddition of cyclohexenones to alkenes has been one of the most intriguing aspects of this reaction, ever since Corey's finding that the major products in several systems appeared to have trans-fused four- and six-membered rings.[3] The structure assignments were typically based on indirect evidence for the most part. In a few cases, the adduct stereochemistry was confirmed by chemical conversion to natural products with known stereochemistry.[1,2] However, in many cases it was not possible to assign cycloadduct stereochemistry unequivocally on the basis of spectroscopic data. The danger of making structural assignments based solely upon NMR coupling constants was clearly pointed out by Lenz.[27] In Rubin's original study of cycloaddition of steroid enones to cyclopentene,[12] the stereochemistry of the ring junction was assigned principally on the basis of ORD and CD data,[30] a method also utilized by Lenz,[27] but the stereochemical relationship of the cyclopentane ring to the steroid nucleus remained undefined. Although cis- and trans-fused bicyclo[4.2.0]octan-2-ones can frequently be distinguished by base-induced epimerization of the trans-fused isomers, Lenz has point out[13] that in some cases trans-fused isomers are remarkably stable under epimerizing conditions, probably because of steric interference.

The spectroscopic data obtained in the present study offered some help in the structure assignments. Generally, J_{cis} values are larger than J_{trans} values for vicinal protons on a cyclobutane ring, although both can vary between 3 and 12 Hz.[31,32] Cis fusion to a six-membered ring favors a planar cyclobutane ring (see Figures 1 and 3) while analogous trans fusion causes puckering in the cyclobutane (see Figures 2 and 4). Thus, trans coupling between two pseudoaxial protons (H–C–C–H dihedral angle > 170°), as in **10**, is larger than trans coupling between two pseudoequatorial protons (H–C–C–H dihedral angle < 170°) as in adduct **1** (Scheme II). Also, coupling of cis protons in planar cyclobutanes should be larger than cis coupling in puckered cyclobutanes. Thus, because of the particularly sensitive dependence of vicinal proton coupling constants in cyclobutanes on the dihedral angle, either cis or trans coupling may be larger depending on the exact conformation of the four-membered ring, and structural assignments made on this basis are not dependable.[23,24,31,32]

In comparison with the ^{1}H NMR spectra of these adducts, the ^{13}C NMR spectra were much more revealing with respect to the stereochemistry. Steric crowding and γ-interactions arising from overlap of van der Waals radii of closely spaced protons cause shielding of the carbons attached to these protons.[18] Thus, comparing adducts **1** and **2** from the addition of cyclohexenone to cyclopentene, the ^{13}C NMR resonances for C-1 (44.0), C-8 (28.9), and C-10 (29.1) in the cis-syn-cis isomer **2** are shifted upfield from the corresponding resonances (47.9, 32.5, and 33.1, respectively) in the cis-anti-cis isomer **1**.

Based on epimerization experiments, it seems that trans-fused cycloadducts of enones are less stable than the corresponding cis-fused compounds, although the former are frequently the major product of photocycloaddition. The lowest energy conformations of the stereoisomeric [2 + 2] cycloadducts derived from 2-cyclohexenone and TME using MACROMODEL[21] are shown in Figure 5. The calculated energies of the cis- and trans-fused adducts **9** and **8** are 44.62 and 47.66 kcal/mol, respectively (ΔE = 3.0 kcal/mol). The energies of the four adducts derived from cyclohexenone and cyclopentene are as follows: **1**, 47.75; **2**, 50.39; **3**, 55.12; **4**, 55.07. Thus, the difference in energies of the two sets of cis- and trans-fused adducts in this case (**1**–**3**; **2**–**4**) are 7.4 and 4.7 kcal/mol, respectively. It is obvious from Figures 4 and 5 that in the trans-fused adducts the six-membered ring is relatively unstrained, assuming a chairlike conformation, with diequatorial linkages to the quite distorted four-membered ring. In the corresponding cis-fused adduct, the six-membered ring assumes a higher energy boat conformation, but the cyclobutane ring is correspondingly less distorted. Obviously, the cyclohexanone ring can incorporate the strain associated with cis fusion at lower energy cost than that associated with the distorted cyclobutane ring in the corresponding trans-fused cycloadducts. Rubin[12] arrived at similar conclusions without the benefit of X-ray structures of his adducts.

A similar picture emerges from consideration of the X-ray structures of the cis- and trans-fused adducts **5b** and **6b** derived from testosterone acetate (TA) and cyclopentene (CP) shown in Figures 1–3. Again, the cyclo-

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(29) Gaudemer, A. In *Stereochemistry: Fundamentals and Methods*; Kagan, A. B., Ed.; Thieme: Stuttgart, 1977; Vol. I, p 85.

(30) Crabbé, P. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden-Day: San Francisco, 1965.

(31) Fleming, I.; Williams, D. H. *Tetrahedron* **1967**, *23*, 2747. Weitkamp, H.; Korte, F. *Tetrahedron Suppl.* **1966**, *7*, 75.

(32) See also: Mintas, M.; Schuster, D. I.; Williard, P. G. *Tetrahedron* **1988**, *44*, 6001.

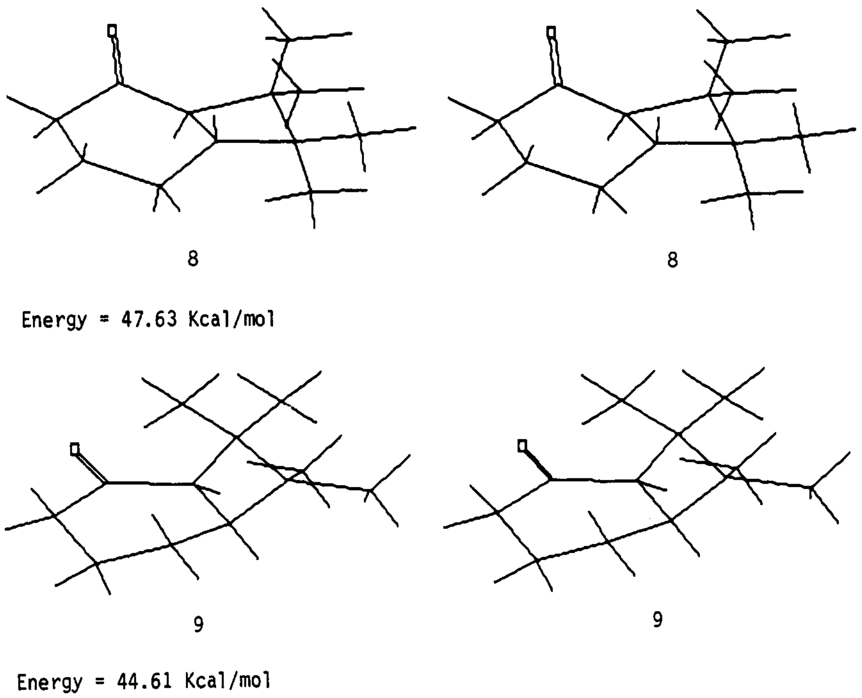

Figure 5. Stereoviews of the minimum energy structures of cyclohexenone–TME adducts 8 and 9 determined using MACROMODEL.

hexanone ring assumes a chair conformation in the trans-fused adduct with diequatorial linkage to the cyclobutane ring, while the cyclohexanone in the cis-fused adduct assumes a boat conformation. As compensation, the cyclobutane ring is again much more distorted in the trans-fused adduct. There is a considerable increase in nonbonded strain in the alternative cis-fused adduct **7b** ($4\beta,5\beta$), which is not formed photochemically and can only be obtained by base isomerization of **6b**. The H–C_4–C_{22}–H dihedral angles in **5b**, **6b**, and **7b** are 137°, 157°, and 10°, respectively, according to the X-ray structures. Unfortunately, because of the complexity of the ^{1}H NMR spectra, it has not been possible as yet to obtain the associated coupling constants to compare with the corresponding values for adducts 1–4.

The formation of adducts **5b** and **6b** involves attack on the less hindered α-face of the planar π,π^* triplet state of TA[10,14,15] by CP with initial bonding apparently to the α-carbon of the enone moiety, since the hydrogen at C-4 has the identical stereochemistry in both these adducts. It seems that the resulting triplet diradical is sufficiently distorted geometrically that ring closure occurs at both the top and bottom face at C-5 to give a mixture of trans- and cis-fused adducts in a process that is clearly subject to kinetic rather than thermodynamic control. It is likely that pyramidalization occurs at C-5 prior to ring closure, most likely at the biradical stage. Quenching studies[33] have established that both cyclopentene and the triplet quencher methylnaphthalene intercept the same triplet excited state of TA in which, as already mentioned, the enone moiety has been concluded to be essentially planar.[10,14,15]

Theoretical calculations[6] indicate that the $^3\pi,\pi^*$ (T_1) state of conformationally flexible conjugated enones, typified by acrolein, adopts a distorted nonplanar geometry by twisting around the C=C bond. For cyclohexenone, an angle of twist of 60° was predicted. An angle of twist of 63.5° at the ring fusion is seen in the X-ray structure of the oxime derivative of the adduct of 2-cyclohexenone and TME (Figure 4). This agreement may be pure coincidence, but it suggests that in nonconstrained systems the conformation of the cyclohexenone in its T_1 state is somehow preserved over the course of the cycloaddition process. It has been established that cyclohexenone triplets have significantly (7–10 kcal/mol) lower energy than constrained enone triplets, consistent with such geometric distortion.[15]

The corresponding angle of twist at the 6–4 ring junction in the trans-fused adduct **6b** from TA and CP is even larger, 72.5°, despite the relative rigidity of the steroid nucleus, demonstrating that twisting in the triplet state is *not* a prerequisite for formation of highly twisted trans-fused adducts. Clearly, a much better picture of what is happening at the biradical stage, especially of the structural factors which affect the competition between cyclization and fragmentation, is necessary before it will be possible to predict the stereochemical course of [2 + 2] photocycloadditions of cyclohexenones with any degree of accuracy.

Experimental Section

Materials and Methods. The following chemicals were used as received: testosterone acetate (Sigma), benzene (Fisher, reagent grade), *n*-hexane and ethyl acetate (Aldrich, HPLC grade), methanol (Aldrich, 99+%, Gold Label), ethanol (USI, anhydrous), ethyl ether (Fisher, purified, anhydrous), hydroxylamine hydrochloride, pyridine, and acetic anhydride (Fisher), and tetramethylethylene (Aldrich). 2-Cyclohexenone and cyclopentene (Aldrich) were purified by vacuum distillation. Acetonitrile (Aldrich) was carefully dried over calcium hydride under a nitrogen atmosphere by either reflux for at least 3 h or extended stirring at room temperature. The acetonitrile was then decanted into a fresh flask and distilled from phosphorous pentoxide using a Vigreux column (bp 81 °C). The dried solvent was stored under nitrogen. Florisil was obtained from Floridin.

^{1}H and ^{13}C NMR spectra were obtained on a General-Electric-Nicolet QE-300 MHz NMR spectrometer. All spectra were obtained in deuterated chloroform, and chemical shifts are given in parts per million relative to tetramethylsilane. Infrared spectra were obtained on a Mattson Polaris FTIR instrument on samples in deuteriochloroform. Gas chromatographic analyses were done using a Hewlett-Packard Model 5710A chromatograph equipped with a capillary column (Alltech, 30 m × 0.25 mm Heliflex RSL-150). The following temperature program was generally

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[33] Brown, P. B. Ph.D. Dissertation, New York University, 1988.

utilized: initial time 0, temperature 100 °C; rate 4 °C/min; final time 25 min, temperature 200 °C. For the TA–CP reaction, the column temperature was varied from 150 to 290 °C at a rate of 32°/min. GC/mass spectra were obtained using a Hewlett-Packard 5992 GC–mass spec system. HPLC was carried out with a Waters Millipore apparatus equipped with a Waters 600E pump and a Waters 410 differential refractometer.

Photoaddition of 2-Cyclohexenone to Cyclopentene. A solution of 0.0288 g (0.3 mmol) of 2-cyclohexenone and 0.3065 g (4.5 mmol) of cyclopentene in 2.5 mL of anhydrous acetonitrile in a Pyrex test tube was irradiated with a Hanovia 450-W lamp for 75 min. The sample was degassed with argon prior to irradiation. After the irradiation, the excess cyclopentene was removed under a stream of nitrogen to yield a yellowish oily mixture of four products according to GC analysis. This sample was then treated for 2 days with 1.25 g of KOH in 5 mL of methanol and 15 mL of water. After being neutralized using dilute aqueous HCl, the mixture was extracted with ethyl ether, and the extracts were subjected to GC/MS analysis. Two products were identified as cyclohexenone–cyclopentene adducts on the basis of their molecular weights and relative GC retention times. These adducts were separated by HPLC using 20:1 hexane–ethyl acetate as the solvent system.

Photocycloaddition of Testosterone Acetate to Cyclopentene. Testosterone acetate (TA, 1.0 g, 3.1 mmol) was irradiated in neat cyclopentene (CP, 9 mL). The sample, which had been previously degassed using nitrogen, was immersed in a water bath and irradiated with a Hanovia 450-W lamp for 14.5 h. The excess cyclopentene was evaporated under a stream of nitrogen, and the resulting white residue was recrystallized from methanol to give a mixture of two products in a ratio of 1:1, according to capillary GC analysis. The mixture could be separated by chromatography on a florisil column. Elution began with 20% hexanes in benzene, and the solvent polarity was increased by gradually decreasing the percentage of hexanes. The cis-fused adduct **5b** was eluted off the column with 10% hexanes in benzene. The solvent system was changed to benzene and then to 3% ethyl acetate in benzene to obtain the trans-fused adduct **6b**. These two adducts were purified by recrystallization from methanol and from hexane, giving crystalline material, mp 226–228 °C and 185–187 °C, respectively. Anal. Calcd for $C_{26}H_{38}O_3$: C, 78.46; H, 9.24. Found for **5b**: C, 78.35; H, 9.13. Found for **6b**: C, 78.25; H, 9.48.

The trans adduct **6b** (300 mg) was epimerized by heating at reflux for 2 days in an ethanolic solution (25 mL) of potassium hydroxide pellets (1 g). The cooled solution was neutralized with dilute HCl and then extracted with ethyl ether. The extracts were dried over $MgSO_4$, after which the ether was removed to give an oil which was flash chromatographed using 5% ethyl acetate in methylene chloride as the eluent. Removal of the solvent gave an oil, which was immediately treated with acetic anhydride (0.8 mL) and pyridine (1.0 mL) for 24 h at room temperature. The excess acetic anhydride and pyridine was removed at reduced pressure to give a yellowish solid (**7b**), which was recrystallized from ether very slowly at room temperature, giving crystals, mp 174–176 °C.

Photoaddition of 2-Cyclohexenone to Tetramethylethylene. A solution of 0.3 g (3.1 mmol) of 2-cyclohexenone and 4.3 g (0.05 mol) of TME in 30 mL of acetonitrile was prepared and degassed under a stream of nitrogen for 10 min. Irradiation in a Pyrex flash was performed using a 450-W Hanovia lamp for 7.5 h, resulting in the formation of two adducts in a ratio of 4:1, according to GC and GC/MS analysis. The major product has been shown previously to be the trans-fused [2 + 2] cycloadduct. Removal of the excess acetonitrile at reduced pressure gave a yellow oil, 114 mg of which was dissolved in 5 mL of ethanol. This solution was added to water (10 mL) containing 1 g of sodium acetate and 0.7 g of hydroxylamine hydrochloride. The mixture was heated at reflux for 2.5 h, after which it was extracted with ether, and the ethereal extracts were dried over $MgSO_4$. The ether was removed under a stream of nitrogen. A crystalline oxime derivative **10**, mp 164–166 °C, was obtained by fractional crystallization very slowly from ether.

X-ray Structural Analysis. All data were collected on a Rigaku AFC-6S diffractometer with graphite monochromated radiation and a 1.5 kW sealed tube generator. The structures were solved by direct methods.[34] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in idealized positions. Refinement converged with agreement factors of $R_1 = \Sigma||F_o| - |F_c||/\sum|F_o|$ and $R_2 = [(\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)]^{1/2}$. The refinement was carried out with the TEXSAN crystallographic software package of Molecular Structure Corporation.[35] An empirical absorption correction (DIFABS) was applied in each case.[36]

Crystal data for cis (4α,5α) adduct **5b** of TA and CP. Formula $C_{26}H_{38}O_3$. Space group $P2_12_12_1$ (no. 19), $a = 15.993$ (4) Å, $b = 17.967$ (4) Å, $c = 7.652$ (3) Å, $V = 2199$ (1) Å^3, $Z = 4$, $D_{cal} = 1.204$ g/cm^3, μ (Cu Kα) = 5.62 cm^{-1}, observed reflections [$I > 2.00\sigma(I)$] 1259, $R_1 = 0.053$, $R_2 = 0.052$.

Crystal data for trans (4α,5β) adduct **6b** of TA and CP. Formula $C_{26}H_{38}O_3$. Space group $P2_12_12_1$ (no. 19), $a = 11.324$ (3) Å, $b = 25.721$ (5) Å, $c = 7.593$ (1) Å, $V = 2211.4$ (8) Å^3, $Z = 4$, $D_{cal} = 1.197$ g/cm^3, μ (Mo Kα) = 0.71 cm^{-1}, observed reflections [$I > 2.00\sigma(I)$] 1774, $R_1 = 0.054$, $R_2 = 0.062$.

Crystal data for cis (4β,5β) adduct **7b** of TA and CP. Formula $C_{26}H_{38}O_3$. Space group $P2_1$ (no. 4), $a = 7.492$ (2) Å, $b = 13.459$ (5) Å, $c = 11.072$ (3) Å, $\beta = 91.92$ (2)°, $V = 1116$ (1) Å^3, $Z = 2$, $D_{cal} = 1.186$ g/cm^3, μ (Mo Kα) = 0.70 cm^{-1}, observed reflections [$I > 2.00\sigma(I)$] 1152, $R_1 = 0.054$, $R_2 = 0.051$.

Crystal data for oxime **10** of CH and TME adduct **8**. Formula $C_{12}H_{21}NO$. Space group $P\bar{1}$ (no. 2), $a = 12.412$ (1) Å, $b = 12.403$ (4) Å, $c = 8.556$ (3) Å, $\alpha = 100.25$ (3)°, $\beta = 107.84$ (4)°, $\gamma = 100.26$ (4)°, $V = 1195$ (1) Å^3, $Z = 4$, $D_{cal} = 1.085$ g/cm^3, μ (Mo Kα) = 0.64 cm^{-1}, observed reflections [$I > 2.00\sigma(I)$] 2508, $R_1 = 0.101$, $R_2 = 0.112$.

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Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, torsion angles, anisostropic thermal parameters, and complete descriptions of the X-ray structure determinations of **5b**, **6b**, **7b**, and **10** (112 pages); observed and calculated structure factors (48 pages). Ordering information is given on any current masthead page.

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(34) Sheldrick, G. M. *SHELXS-86 in Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University: Oxford, 1985; pp 175–189.

(35) TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation, The Woodlands, Texas, 1985.

(36) Walker, N.; Stuart, D. *Acta Crystallogr. A* **1983**, *39*, 158.