a residue, which was purified by silic gel column chromatography to afford 41.2 mg (83%) of **15** as a colorless oil: $[\alpha]^{25}_D$ +10.5° (*c* 2.1, MeOH); IR (neat) 3450 (NH), 1610, 1510 cm^{-1}; ^1H NMR δ 0.87 (3 H, t, J = 6 Hz), 1.0–1.9 (20 H, m), 4.25 (1 H, t, J = 6 Hz), 6.4–7.4 (10 H, m); MS m/z (relative intensity) 337 (M^+, 5), 182 (100); found m/z 337.2765, calcd for $C_{24}H_{35}N$ (M) 337.2767.

Acknowledgment. We are grateful to Professor Naomichi Furukawa, Tsukuba University, for his helpful discussions. We also thank Dr. Mikio Takeda, Tanabe Seiyaku Co., Ltd., for elemental analysis and Noriko Sawabe and Tomoko Akiyama of this laboratory for NMR and MS measurements. This work was supported in part by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged.

Cycloaddition Reactions of Bisallenes. Stereochemistry of the (4 + 2) Cycloaddition Process

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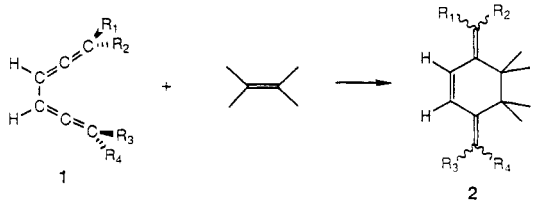
The cycloaddition of *erythro*- and *threo*-8,8-dimethyl-2,3,5,6-nonatetraene (**11e** and **11t**) with *N*-phenylmaleimide has been investigated. The (4 + 2) cycloaddition reactions are stereospecific; **11e** producing only **12**, and **11t** producing only **13**. The dienophile approaches the less sterically hindered face of the bisallene undergoing a symmetry-allowed (2 + 4) cycloaddition, with the groups at the termini of the bisallene on the opposite face of the bisallene rotating outward in a disrotatory manner. The direction of the rotatory motion of the two termini of the bisallene is not controlled by orbital symmetry. The preference for the anti outward disrotatory motion of the termini of the bisallene is attributed to the development of better overlap between the terminal 2p AO's of the interacting diene and dienophile in the transition state for the cycloaddition process and, to a lesser extent, the relief of steric congestion relative to the other rotatory processes.

Introduction

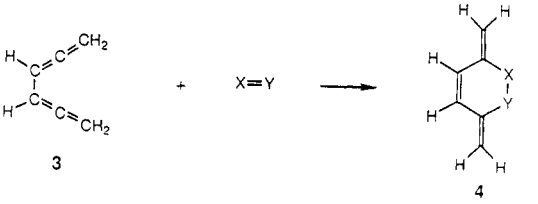
Substituted 1,2,4,5-tetraenes **1** (bisallenes)[1] are a highly reactive, intriguing class of compounds. They not only contain two allene chromophores, but they also contain a central conjugated butadiene chromophore. Thus, substituted bisallenes might be expected to exhibit chemical properties of both substituted allenes and substituted 1,3-butadienes. One such type of reaction of synthetic interest is the (4 + 2) cycloaddition across the central 1,3-butadiene chromophore. With substituted bisallenes, this is a very interesting reaction from a stereochemical point of view. The groups attached to the termini of the bisallene (illustrated in **1**) are oriented perpendicular to the general plane of the butadiene chromophore both of which, during a (4 + 2) cycloaddition process, must undergo a rotation of 90° during the formation of the product **2**. The important question is, in which directions do the



1 **2**

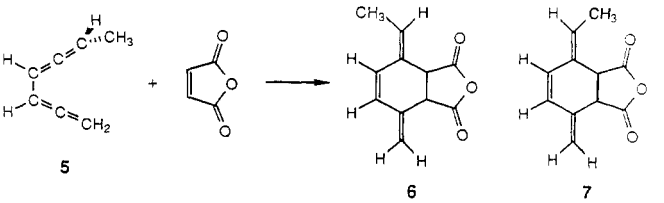
two termini rotate, and are the directions coordinated? The answer to this question does not appear to have unambiguously answered for the (4 + 2) cycloaddition reactions.

A number of cycloaddition reactions of the parent bisallene, 1,2,4,5-hexatetraene (**3**) with a wide range of substituted dienophiles has been described.[2] Apparently the



3 **4**

only concerted (4 + 2) cycloaddition reaction of an unsymmetrically substituted bisallene is that of **5** with maleic anhydride, which is reported to produce only **6**.[2] The stereochemistry of **6** was assigned on the basis of extensive NMR chemical shift studies, which showed that the effect of added chemical shift reagent on the chemical shift of the methyl groups was very small compared to the effect on the vinyl hydrogens syn to the anhydride moiety. None of the stereoisomeric cycloadduct **7** was detected in the cycloaddition reaction product mixture. It was suggested that the dienophile approached from the less sterically hindered side of the bisallene in the syn conformation, with an outward rotation of the methyl group on the opposite face of the bisallene occurring to produce the observed product.[2] The proposed disrotatory motation was based



5 **6** **7**

on the observed stereochemistry of the cheleotropic (4 + 1) addition of sulfur dioxide to a number of substituted bisallenes reported earlier which occurred by approach to the less sterically hindered face of the bisallene with

(1) Although the bisallenes are shown in their s-cis conformations, the lowest energy conformations are the s-trans conformations (D. J. Pasto, results of unpublished theoretical calculations).

(2) Hopf, H.; Schon, G. *Annalen* **1981**, 165.

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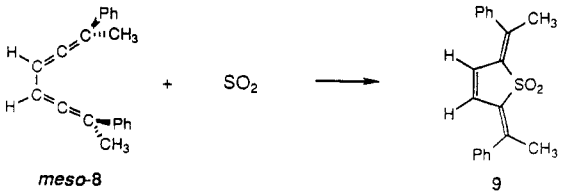
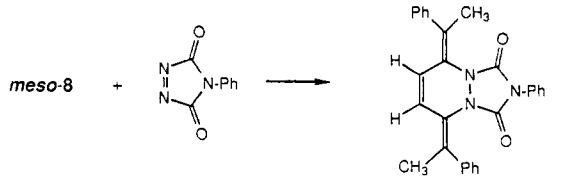
outward disrotatory motion of the groups anti to the approaching sulfur dioxide as illustrated in the addition of sulfur dioxide to *meso*-8.[3] The cycloaddition of the highly



meso-8 9

reactive dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (NPTD) to several terminally tetrasubstituted bisallenes has been reported.[4] The cycloaddition of NPTD to *meso*-8 produces only adduct **10** in rather low yield (extensive ene product formation is also observed).[4] In this case anti outward disrotatory motion is not observed, leading the authors to suggest that the cycloaddition does not occur via a concerted process.[4]



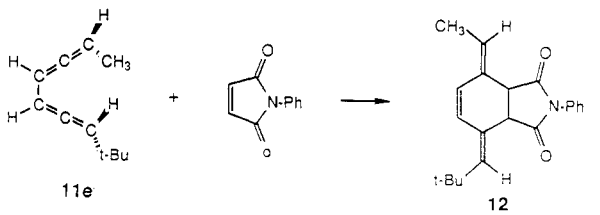
10

No example of a concerted cycloaddition to both stereoisomers of a bisallene has been reported. In the present study the stereochemistry of the cycloaddition of *N*-phenylmaleimide to *erythro*- and *threo*-8,8-dimethyl-2,3,5,6-nonatetraene[5] (**11e** and **11t**) has been determined, and an explanation is provided for the observed disrotatory motion that occurs during the cycloaddition process.

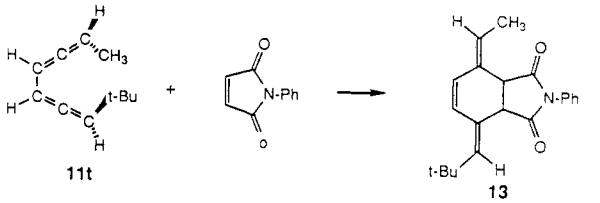
Results

The palladium(0)-catalyzed coupling of (3-*tert*-butylallenyl)zinc chloride with 3-bromo-1-butyne produces a mixture of *erythro*- and *threo*-**11** (**11e** and **11t**) in a 59.9:40.1 ratio.[6] When a quantity of this mixture is stirred with an amount of *N*-phenylmaleimide (NPMI) equivalent to the amount of **11e** present, the **11e** is essentially completely reacted leaving essentially pure unreacted **11t** and only the (4 + 2) cycloadduct **12**. Isolation of the pure **11t** followed by further reaction with NPMI very slowly produces only the single cycloadduct **13**.

The assignment of the stereochemistry about the double bonds bearing the *tert*-butyl groups in **12** and **13** is based on the following considerations. In the cycloaddition reaction of **5** with maleic anhydride, the methyl group, the largest group attached to the termini of the bisallene, ends up trans to the anhydride moiety. As indicated above, the stereochemistry of **6** has been assigned on the basis of the relative changes in the chemical shifts of the various

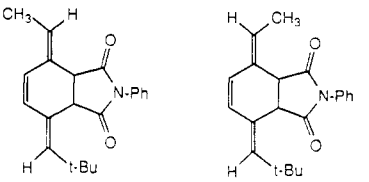


11e 12



11t 13

protons in **6** in the presence of a chemical shift reagent.[2] Also, the observed chemical shift of the vinyl methyl group was interpreted in terms of being oriented away from the strongly deshielding proximate carbonyl group.[2] In the cycloaddition of **11e** and **11t** with NPMI the *tert*-butyl group is also expected to end up in the orientation shown in **12** and **13**. The long-range coupling constants between H_5 and H_6 in **12** and **13** of 1.32 and 1.59 Hz are consistent with the syn stereochemical relationship between these hydrogens. Unfortunately, cycloadducts having the stereochemistry about the *tert*-butyl-substituted double bond as shown in **14** and **15** are not formed in the cycloaddition



14 15

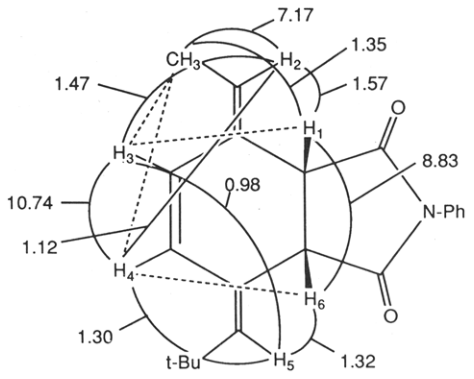
reactions of **11e** and **11t** with NPMI and are not available for a direct comparison of the NMR parameters with those of **12** and **13**. The only experimental evidence in support of the assigned stereochemistry of the *tert*-butyl-substituted double bond is that when the cycloadducts **12** and **13** are heated in solution in the presence of iodine no isomerization is observed. Should the stereochemistry about the *tert*-butyl-substituted double bonds be that shown in **14** or **15**, isomerization about the double bonds should occur to produce the less sterically congested cycloadducts **12** and **13**.

The assignment of stereochemistry about the methyl-substituted double bond in **12** and **13** has been assigned on the relative chemical shifts of the vinyl methyl groups, and the long-range coupling constants between H_1 and H_2, and H_1 and the methyl protons. In **13** the methyl group appears at lower field (δ 1.94) than that in **12** (δ 1.82), indicating that the methyl group in **13** is deshielded to a greater extent by the proximate carbonyl group than in **12**. In addition, the larger syn long-range allylic coupling constant of 1.57 Hz between H_1 and H_2 in **12** relative to that in **13** (1.22 Hz) and the larger anti homoallylic coupling constant of 1.35 Hz in **12** relative to that in **13** (0.7 Hz) are also consistent with the assigned stereochemistry about the methyl-substituted double bond.

Discussion

The results show that cycloadduct **12** is formed only from **11e**, and **13** only from **11t**. In both cases the cycloadducts are formed in concerted ($_\pi2_s + _\pi4_s$) cycloaddition processes by the approach of the NPMI to the *less hindered face* of **11e** and **11t**, as shown in the s-cis confor-

(3) Kleveland, K.; Skattebol, L. *Acta Chem. Scand.* **1975**, *B29*, 827.
(4) Boan, C.; Skattebol, L. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1568.
(5) The designation of *erythro* and *threo* to the two stereoisomers of **11** is an extension of the use of these terms in simpler systems. In a system containing two adjacent chiral centers, in the classic sense two carbon atoms, the *erythro* isomer is designated as the stereoisomer having the configurations corresponding to erythrose; i.e. when the two sets of identical ligands are eclipsed, and the dissimilar set of ligands are also eclipsed. Similarly, the *threo* isomer corresponds to the configurations in threose in which only one set of identical, or dissimilar, ligands are eclipsed. In **11e** and **11t** there are also two adjacent chiral centers; the two chiral allene chromophores. Thus, the terms *erythro* and *threo* also apply to the isomers of **11**. In a more subtle sense, the use of *erythro* and *threo* imply the existence of *d,l* pairs of stereoisomers, which is the case with **11e** and **11t**. The use of anti and syn, or cis and trans, do not imply these stereochemical relationships.
(6) Ruitenberg, K.; Kleijn, H.; Westmijze, Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 405.



12

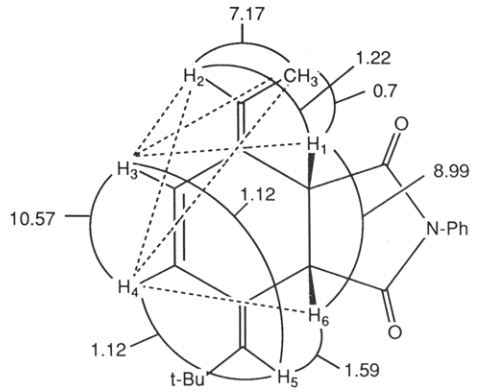


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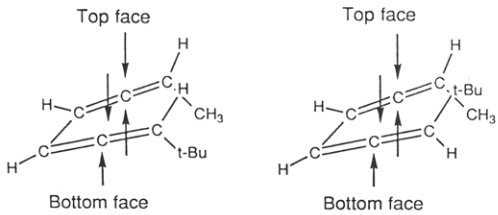
Figure 1. The coupling constants measured in **11e** and **11t** by the use extensive double-resonance experiments. The coupling interactions that were too small to be resolved but were detected by line narrowing in the double resonance experiments are indicated by dashed lines.



11e **11t**

Figure 2. The illustration of the steric interactions generated on approach to the two faces of **11e** and **11t**.

mations of **11e** and **11t** in Figure 2, with *exclusive outward disrotatory motion* of the groups anti to the approaching NPMI. In the approach of NPMI to the top face of **11e** in an endo cycloaddition configuration the vinyl hydrogens of NPMI will encounter the two terminal bisallene hydrogens that project up toward the approaching NPMI, whereas in the approach to the bottom face of **11e** the vinyl hydrogens of NPMI will encounter the methyl and *tert*-butyl groups which project downward toward the approaching NPMI. Thus, the approach of the NPMI to the top face of **11e** is greatly sterically favored over the approach of NPMI to the bottom face of **11e**. In the reaction of NPMI with **11t**, adverse steric interactions will be encountered during the approach of NPMI to either face of the bisallene. During the approach from the top side one of the vinyl hydrogens of NPMI will encounter the *tert*-butyl group, while in the approach to the bottom side one of the vinyl hydrogens of NPMI will encounter the methyl group. As the methyl group is considerably smaller than the *tert*-butyl group, the approach of NPMI to the bottom side is expected to be greatly favored. If one compares the

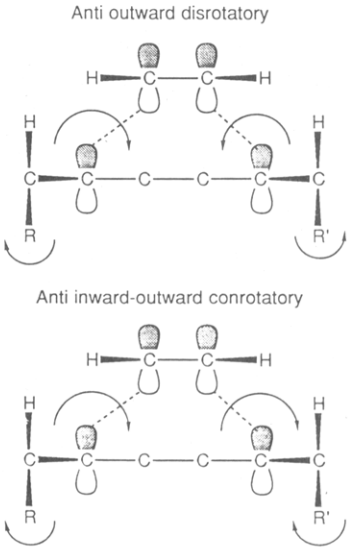


Figure 3. The illustration of the orbital interactions on anti outward disrotatory (top) and anti inward–outward conrotatory (bottom) motions of the terminal groups of a bisallene. The 2p AO's shown in the figure are those at the termini of the interacting π systems of the diene and dienophile. The in-plane, terminal π systems of the bisallene are not shown.

steric interactions in the more favorable approaches to **11e** and **11t**, the approach to the top face of **11e** should be significantly favored over approach to the bottom face of **11t**. It is this difference in steric interactions that results in the observed significantly greater reactivity of **11e** relative to **11t** toward cycloaddition with NPMI.

What are the factors that lead to the exclusive anti outward disrotatory motion of the groups attached to the termini of the bisallene on the face of the bisallene opposite the approaching NPMI? An analysis of the orbital symmetry correlations between the terminal π systems of the bisallene and the triene system of the cycloadducts shows that both conrotatory and disrotatory motions are allowed; thus, orbital symmetry does not play a role in determining the direction of rotation of the two termini of the bisallene.

There are two factors that appear to favor the observed anti outward disrotatory process compared to other possible processes. The first is steric in origin. The anti inward disrotatory motion of the R and R′ groups will ultimately produce the more sterically congested product, although early along the reaction coordinate these steric interactions must be very small because of the large distance between R and R′ and the NPMI. The anti outward disrotatory motion will produce a minimum of adverse steric interactions and, thus, will be favored. Either of the anti inward–outward conrotatory motions, shown in the lower part of Figure 3, will be intermediate in terms of the degree of steric interactions.

The second factor is an electronic one. During the anti outward disrotatory motion, the 2p AO's at the termini of the butadiene chromophore undergoing the cycloaddition process will rotate inward toward the 2p AO's of the approaching dienophile (shown in the top part of Figure 3). This motion will increase the overlap between the 2p AO's of the interacting π systems, thus favoring this mode of rotation. The anti inward disrotatory motion of R and R′, the opposite direction of rotation compared to that shown in the top part of Figure 3, will result in an outward rotation of the 2p AO's at the termini of the butadiene chromophore, which will result in the reduction of the overlap between the interacting 2p AO's of the two π systems. In the anti inward–outward conrotatory process (shown in the lower part of Figure 3), one 2p AO of the

butadiene will rotate inward, resulting in increased overlap, but the other 2p AO will rotate outward, resulting in a reduction of the overlap. Overall, this should result in a less favorable process than in the case of the observed anti outward disrotatory motion, but better than in the anti inward disrotatory process. It is believed that this electronic factor is the dominant factor which controls the direction of rotation of the two termini of a bisallene in a concerted (4 + 2) cycloaddition process.

Experimental Section

Reaction of a Mixture of *erythro*- and *threo*-8,8-Dimethyl-2,3,5,6-nonatetraene (11e and 11t) with *N*-Phenylmaleimide. A solution of 22.8 mg of a 59.9:40.1 mixture of **11e** and **11t** (0.154 total mmol with 0.092 mmol of **11e**) and 16.0 mg (0.092 mmol) of *N*-phenylmaleimide in 1.5 mL of $CDCl_3$ in a capped NMR tube was maintained at 25 °C for 22 h. The NMR spectrum was recorded showing the presence of essentially pure **11t** (less than 1% of **11e** remained unreacted) and essentially only the one (4 + 2) cycloadduct **12** present (less than 2% of **13** was present in the reaction mixture). The pure **11t** was isolated by chromatography on a short silica gel column eluting with 95:5 Skelly B–ether, along with essentially pure **12**: NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9 H, *t*-Bu), 1.82 (dd, J = 7.17, 1.35 Hz with unresolved coupling to H_3 and H_4, 3 H, CH_3), 3.67 (dd, J = 8.83, 1.32 Hz with unresolved coupling to H_4, 1 H, H_6), 3.79 (ddq, J = 8.83, 1.57, 1.35 Hz with unresolved coupling to H_3, 1 H, H_1), 5.77 (ddd, J = 1.31, 1.30, 0.98 Hz, 1 H, H_5), 5.94 (qddd, J = 7.17, 1.57, 1.47, 1.12 Hz, 1 H, H_2), 6.45 (ddd, J = 10.74, 1.30, 1.12 Hz with unresolved coupling to the CH_3 and H_6, 1 H, H_4), 7.0–7.7 (m, 5 H, aromatic H); MS (on mixture) m/e 321.

Cycloaddition of 11t with *N*-Phenylmaleimide. The pure **11t** isolated from the above experiment was dissolved in 1.5 mL of $CDCl_3$. A slight excess of NPMI was added, and the solution was allowed to stand at 25 °C for 5 days. Analysis by NMR showed the presence of unreacted **11t** and NPM, and the presence of a single cycloadduct, **13**, which was isolated by chromatography on a small silica gel column eluting with 95:5 Skellysolve B–ether: NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9 H, *t*-Bu), 1.94 (dd, J = 7.17, 0.7 Hz with unresolved coupling to H_3, 1 H, CH_3), 3.73 (dd, J = 8.99, 1.59 Hz with unresolved coupling to H_4, 1 H, H_6), 4.19 (ddq, J = 8.99, 1.22, 0.7 Hz with unresolved coupling to H_3, 1 H, H_1), 5.87 (ddd, J = 1.59, 1.12, 1.12 Hz, 1 H, H_5), 5.92 (qd, J = 7.17, 1.22 Hz with unresolved coupling to H_3, 1 H, H_2), 6.13 (dd, J = 10.57, 1.12 Hz with unresolved coupling to CH_3, H_1 and H_2, 1 H, H_3), 6.54 (dd, J = 10.57, 1.12 Hz with unresolved coupling to CH_3, H_2 and H_6, 1 H, H_4), 7.0–7.7 (m, 5 H, aromatic H).

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the partial support of this research and to the National Science Foundation for partial support (NSF Grant No. CHE-8709725).

Notes

Synthesis of (±)-Marmelo Oxides by a Radical Cyclization Reaction

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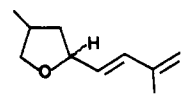
Marmelo oxides A and B (**1**), irregular monoterpenes, are characteristic flavor components of the quincefruit (*Cydonia oblonga*) isolated by Tsuneya et al. together with marmelolactones A and B (**2**).[1] The relative (A as cis and B as trans) as well as absolute stereochemistry was established by Nishida et al. by converting marmelolactones (**2**) to oxides **1**.[2] Currently the radical cyclization reaction is widely accepted as a powerful tool in organic synthesis.[3] In continuation of our interest in the application of radical cyclizations to various furanoid compounds,[4] we now describe a route to marmelo oxides A and B (**1**), based on a radical cyclization reaction.

The synthetic sequence is depicted in Scheme I; radical cyclization of the bromo alcohol **3** generates the tetrahydrofuran **5**, which on oxidation followed by Wittig olefination results in the target **1**. Thus, dispersion of *N*-bromosuccinimide in allyl alcohol furnished the requisite bromo alcohol **3** in 55% yield. The key radical cyclization of the bromo alcohol **3** was carried out by using in situ generated[5] catalytic tri-*n*-butyltin hydride (from *n*-Bu_3SnCl and $NaCNBH_3$ in *t*-BuOH)[4] in the presence of a catalytic amount of AIBN, and the cyclized alcohol **5** was obtained in 43% yield as a 1:3 mixture (by NMR) of cis and trans isomers. The radical cyclization was found to be efficient with the corresponding acetate **4** (68% yield). The oxidation of the alcohol **5** was tried with a variety of reagents, but we were unable to isolate the aldehyde **7**, probably due to the instability of **7**. We finally resorted to Ireland's procedure[6] of trapping the aldehyde **7** with Wittig ylides. Swern oxidation (ClCOCOCl, DMSO, NEt_3) followed by the addition of (carbethoxymethylene)triphenylphosphorane (or acetonylidenephosphorane) furnished the olefins **8** and **9**, with excellent *E* selectivity (NMR), albeit in low yields. Application of Taber's modification[7] (P_2O_5, DMSO, NEt_3) followed by the addition of Wittig ylides, however, generated the olefins **8** and **9** in respectable yields (65% and 50%). It is worth mentioning, in the synthesis of Nishida et al. via marme-



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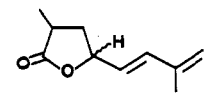

2

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