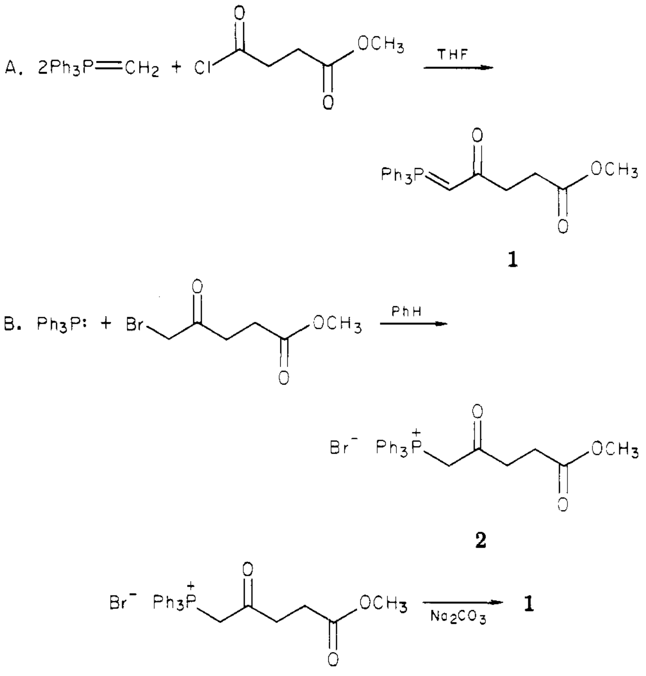
Scheme I



Scheme II

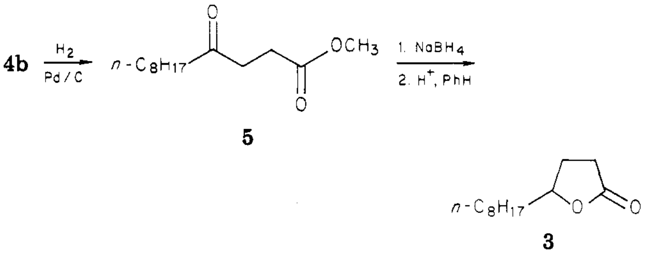
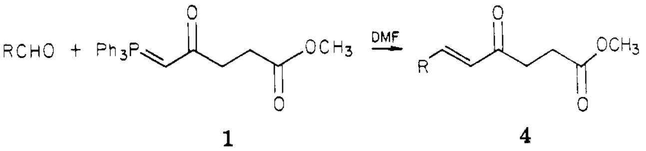
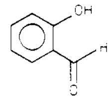
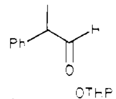
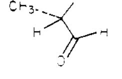
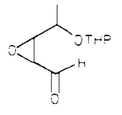


Table I



aldehyde	temp, °C	time	product	% yield[a,b]
PhCHO	55	2 days	4a	90
n-C$_6$H$_{13}$CHO	reflux	2 days	4b	71
	25	24 h	4c	70
	65	2 days	4d	80
	65	24 h	4e	87
	25	18 h	4f	93

[a] All products gave satisfactory elemental analysis and exhibited consistent spectral properties. [b] All yields are unoptimized.

tential for application to butanolide synthesis. Details of other reactions of ylide **1**, and total synthesis of other, dissimilar, natural products will be reported in due course.

Acknowledgment. We thank the Boeing Co. for their generous support in the purchase of the 200-MHz spectrometer.

Registry No. **1**, 84028-77-3; **2**, 84028-78-4; (±)-**3**, 57084-18-1; **4a**, 84028-79-5; **4b**, 84028-30-8; **4c**, 84028-81-9; **4d**, 84028-82-0; **4e**, 84028-83-1; **4f**, 84028-84-2; **5**, 33566-59-5; Ph$_3$P=CH$_2$, 3487-44-3; Ph$_3$P, 603-35-0; PhCHO, 100-52-7; n-C$_6$H$_{13}$CHO, 111-71-7; 3-carbomethoxypropionyl chloride, 1490-25-1; methyl 5-bromolevulinate, 53856-93-2; salicylaldehyde, 90-02-8; α-methylbenzeneacetaldehyde, 93-53-8; (*S*)-2-[(tetrahydropyran-2-yl)oxy]-propionaldehyde, 76438-34-1; 2-[[1-(tetrahydropyuran-2-yl)oxy]ethyl]oxiranecarboxyaldehyde, 84028-85-3.

Supplementary Material Available: Experimental procedures for preparation of compounds **1**–**3** and **5**, plus a general procedure for aldehyde homologation, and NMR, IR, and analytical data for **1**, **2**, **4a**–**f**, and **5** are included (3 pages). Ordering information is given on any current masthead page.

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Received September 15, 1982

Stereocontrolled Synthesis of (±)-Modhephene via the Weiss Reaction[1]

Summary: A stereocontrolled synthesis of (±)-modhephene (**1**) has been realized. The key steps were the facile generation of the [3.3.3] propellane system **7** via the Weiss reaction and the stereospecific incorporation of the chiral methyl function into the modhephene skeleton by addition of (dimethylcopper)lithium to the strained, diactivated cyclopropyl ketone **6**. Alkylation of the resulting enolate provided the tetramethyl derivative **12**, which was converted to **1** in three routine steps.

Sir: Modhephene (**1**), the first carbocyclic propellane from a natural source, was isolated by Zalkow in 1978[2] and soon attracted considerable synthetic interest.[3-8] In 1979[9] we proposed to synthesize **1** by an approach that was designed to be completely stereocontrolled. Our route was based on the preparation of the strained, monoactivated cyclopropyl ketone **2**, which would permit regiospecific incorporation of the *gem*-dimethyl group (see **3**), followed by stereospecific introduction of the isolated methyl function of **4** with (dimethylcopper(I))lithium. The introduction of the fourth methyl group by alkylation of the enolate from the cyclopropane opening and the conversion of the ketone into an olefin were to complete the synthesis as illustrated in Scheme I. Although the opening of monoactivated cyclopropanes (especially, strained ones) has

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(1) Dedicated to Dr. Ulrich Weiss, National Institutes of Health, on the occasion of his 75th birthday.

(2) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D. *J. Chem. Soc., Chem. Commun.* **1978**, 420.

(3) Smith, A. B.; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845. Smith, A. B.; Jerris, P. J. "Abstracts of Papers", 179th National Meeting of the American Chemical Society, Houston, TX, March 24–28, 1980; American Chemical Society: Washington, DC, 1980; ORGN 63.

(4) Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1980**, *21*, 4569.

(5) Schostorez, H.; Paquette, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 722.

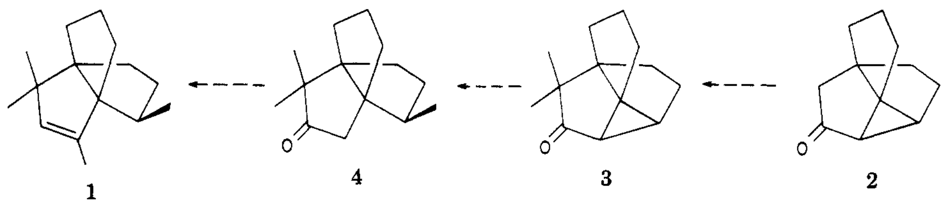
(6) Oppolzer, W.; Marazza, F. *Helv. Chim. Acta* **1981**, *64*, 1575.

(7) Oppolzer, W.; Battig, K. *Helv. Chim. Acta* **1981**, *64*, 2489.

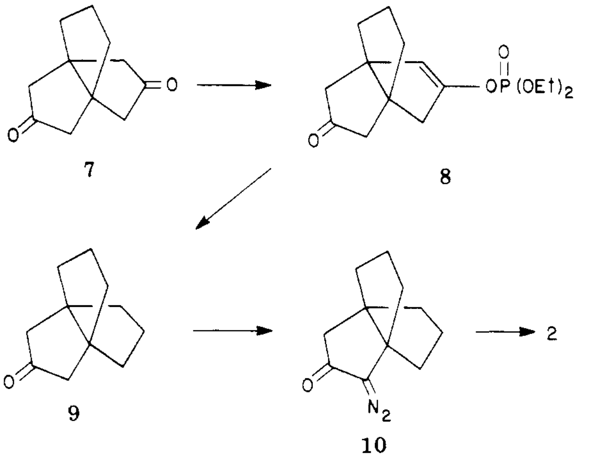
(8) Wender, P. A.; Dreyer, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 5805.

(9) Mitschka, R.; Gawish, A.; Wieringa, C.; Weiss, U.; Cook, J. M. "Abstracts of Papers", presented at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 10–14, 1979, American Chemical Society: Washington, DC, 1979; ORGN-146.

Scheme I



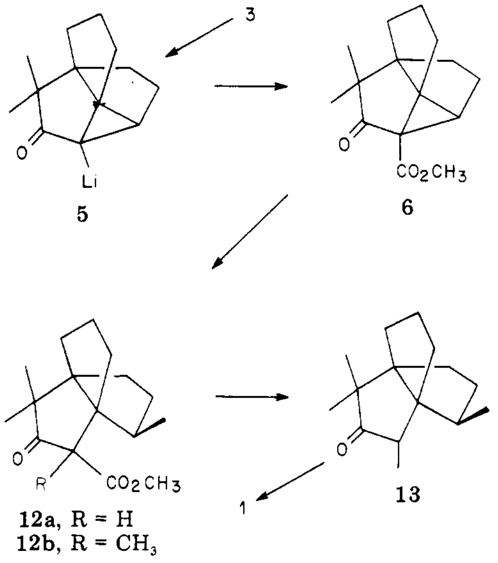
Scheme II



some precedent,[10] it proved to be impossible to open **2** with copper reagents.[11] Therefore, a second activating (methoxycarbonyl) group was added, via the intermediacy of the novel α-lithio ketone **5** (vide infra). Keto ester **6** was opened smoothly by (dimethylcopper(I))lithium, allowing the synthesis to be completed as planned.

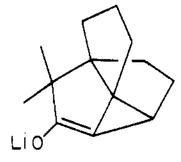
The starting material, dione **7**, was prepared from cyclopentane-1,2-dione and dimethyl 3-oxoglutarate by the Weiss reaction.[12] It was converted in 75% yield to the monoketone **9**[13] via enolphosphonate **8** by the method of Coates,[14] which was followed by formation of the diazo ketone **10** (70% yield), using standard techniques, as shown in Scheme II.[15] Copper sulfate in refluxing toluene was employed[16] to convert **10** into **2**, high dilution being necessary to obtain reproducible yields (68–76%). The construction of the strained cyclopropyl ketone permitted regiospecific incorporation of the *gem*-dimethyl group by simply heating **2** with 2 equiv of methyl iodide in the presence of *tert*-butoxide and HMPA to give **3** in 90% yield. Cyclopropyl ketone **3** was converted in 65% overall yield to the doubly activated species **6** (Scheme III) by sequential treatment with *t*-BuLi, CO_2, HCl, and CH_2N_2.

Scheme III



12a, R = H
12b, R = CH_3

The flanking *gem*-dimethyl group protects the carbonyl of **3** from the usual addition reactions of alkyllithiums. Instead, the *t*-BuLi abstracts the α proton, a process activated by the keto and cyclopropyl groups. Although the proton removed is adjacent to a ketone, the reactive intermediate is not an enolate, for the dihedral angle between the C–H bond broken and the p orbitals normal to the plane of the carbonyl group is ~50°,[17] precluding effective overlap. Even if the overlap were more favorable, the alternative enolate structure **11** contains a trans double bond in a six-membered ring, which due to strain energy is a very unfavorable configuration (i.e., it violates "Bredt's rule").[18] The only good precedent for **5** is the recent report of a bridgehead carbanion stabilized by an amide group in a bicyclomycin precursor,[19] although H–D exchange has been observed in several special cases.[18] Other classic bridgehead carbanions include those stabilized by sulfonyl groups[20] and perfluoroalkane groups,[21] for which p-orbital overlap is not an issue.



11

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(10) Finch, M.; Robert, S. M.; Woolley, G.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1725. Johnson, C. R.; Dhanoa, D. S. *J. Chem. Soc., Chem. Commun.*, **1982**, 358.

(11) For reagents tried, see: ref 3. Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401. Clive, D. L. J.; Farina, V.; Beaulieu, P. *J. Chem. Soc., Chem. Commun.* **1981**, 683. Note that the α' positions of ketone **3** do not bear protons. In all other cases where a monoactivated cyclopropane could not be opened, α' protons were present that allowed rapid enolate formation; see House, H. O.; Prabhu, A. V.; Wilkins, J. M.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 3067. The α (cyclopropyl) proton of ketones such as **3** are not easily removed; vide infra, especially ref 18.

(12) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, 4885. Weber, R. W.; Cook, J. M. *Can. J. Chem.* **1978**, *56*, 189.

(13) All new compounds had correct microanalytical or exact MS data and exhibited consistent ^1H NMR, ^{13}C NMR, IR, and mass spectra.

(14) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765.

(15) Eistert, B. et al., "Methoden der Organischen Chemie"; Mueller, E., Ed.; Georg Thieme: Stuttgart, 1968; Vol. 10, Part 4, p 474. Regitz, M. *Tetrahedron Lett.* **1967**, 1403. Rosenberger, M.; Yates, P.; Hendrickson, J. B.; Wolf, W. *Ibid.* **1964**, 2285.

(16) Yates, P.; Crawford, R. J. *J. Am. Chem. Soc.* **1966**, *88*, 1562. Kirmse, W. "Carbene Chemistry"; Academic Press: New York, 1971; p 259 and references therein. See also Chakrabarti, J. K.; Szinai, S. S.; Todd, A. *J. Chem. Soc. C* **1970**, 1303.

(17) Measured with use of Dreiding models. The barrier to rotation about the C–C double bond of lithioisobutyrophenone is >27 kcal/mol: Jackman, L. M.; Haddow, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 3687.

(18) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. *N.B* Shea's ref 34 and 35.

(19) Williams, R. M. *Tetrahedron Lett.* **1981**, *22*, 2341.

(20) von Doering, W. E.; Levy, L. K. *J. Am. Chem. Soc.* **1955**, *77*, 509. Paquette, L. A.; Meisinger, R. H.; Gleiter, R. *J. Am. Chem. Soc.* **1973**, *95*, 5414.

(21) Brown, P. J. N.; Stephens, R.; Tatlow, J. C.; Taylor, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 937.

(Dimethylcopper(I))lithium smoothly converted **6** into **12a**, which was subsequently alkylated with methyl iodide/KO-*t*-Bu to afford the tetramethyl derivative **12b** in 85% yield. Removal of the methoxycarbonyl group was best accomplished by treatment with lithium iodide in hot γ-collidine,[22] which gave a 95% yield of a mixture of diastereomers, represented by **13**. The cuprate addition occurred with complete stereospecificity; for treatment of **13** with lithium diisopropylamide followed by diethoxyphosphoryl chloride[14] gave only one compound, **14**, in better than 80% yield. Attempts to convert the enolphosphonate into (±)-modhephene by the lithium–ammonia procedure of Ireland[23] met with only limited success; therefore, the ketone **13** was reduced to a mixture of epimeric alcohols, which was then dehydrated with bis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)diphenylsulfurane[24] to afford **1** as the sole product in greater than 60% yield from **13**. The spectra of synthetic modhephene **1** were identical in all respects with the spectra of **1** provided by Professors Smith,[3] Wender,[8] and Zalkow.[2]

We believe this route to modhephene illustrates the synthetic potential of bridgehead keto carbanions such as the one introduced here.

Acknowledgment. We thank Professors Wender, Smith, and Zalkow for providing copies of spectra **1** for comparison purposes. Special thanks are due to Dr. U. Weiss for his interest and encouragement and Professor W. von E. Doering for a stimulating discussion. Professor J. C. Martin kindly supplied the sulfurane used in the last step. We also thank the National Science Foundation (CHE-7910302) for generous financial support.

Supplementary Material Available: Experimental details are available (10 pages). Ordering information is given on any current masthead page.

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[22] Elsinger, F. *Org. Synth.* **1965**, *45*, 7.

[23] Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145. Fetizon, M.; Jurion, M.; Anh, N. T. *J. Chem. Soc., Chem. Commun.* **1969**, 112.

[24] Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

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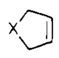
An Indirect Method for Engaging Unactivated Alkenes as Effective Dienophiles in Regioselective Diels–Alder Reactions

Summary: Terminal alkenes and cyclic olefins can be made to enter into efficient, regiocontrolled Diels–Alder cycloaddition by prior selenosulfonation and oxidation to the vinyl sulfone. Reductive desulfonation after condensation with an activated diene provides the formal adducts.

Sir: Although Diels–Alder cycloadditions are among the most versatile and preparatively useful reactions currently available, their scope would be profitably augmented if unactivated olefins could be made to serve as dienophiles.[1] Superpositioning of regioselective control, where appropriate, would enhance matters still further. As a simple solution to this problem, we have made use of a mild, position-selective method for replacing a vinyl proton by a phenylsulfonyl group. The resulting vinyl sulfones are sufficiently reactive[2,3] to enter into annulation reactions and to allow for site-specific attachment of appendages and/or functional groups to six-membered rings. Since subsequent removal of the activating group is readily accomplished, an entire domain of previously inaccessible synthetic methodology now becomes available. In this report, we draw particular attention to the rapid elaboration of 4,5-annulated and 5-substituted cyclohexenones, compounds otherwise accessible only indirectly.[4]

The process for cycloannulation is typified by the conversion of 2,5-dihydrofuran (**1a**) and cyclopentene (**1b**) to **4a** and **4b**, respectively. Irradiation of **1a** and phenylselenenyl benzenesulfonate[5] in CCl_4 solution with 2537 Å lamps[6] effected selenosulfonation and afforded, after direct hydrogen peroxide oxidation of the adduct, the crystalline vinyl sulfone **2a** (75%).[7] Heating of **2a** with (*E*)-1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene[8] in xylene for 28 h followed by mild acid hydrolysis produced **3a** (69%). The conversion to **4a** (83%) was achieved by reduction with zinc dust in acetic acid.[9] The same easily workable sequence led from **1b** to **4b** in 30% overall yield.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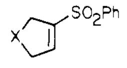
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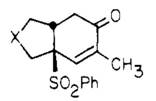
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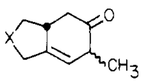
4

a, X = O ; b, X = CH_2

Since orientational dominance is exerted by the sulfonyl group, one can arrive cleanly at 5-substituted cyclohexenones by taking advantage of the anti-Markovnikov manner in which the selenolsulfonate adds to a terminal alkene under photochemical conditions. Thus, treatment of phenyl allyl ether as before delivers **5** cleanly and efficiently (89%). Diels–Alder reaction of **5** with the same unsymmetrical dienophile afforded adduct **6** (68%) from which **7** was obtained (78%). In similar fashion, 1-hexene was transformed via **8** (65%) and **9** (68%) to **10** (78%).

---

[1] Norbornenes (Cava, M. P.; Scheel, F. M. *J. Org. Chem.* **1967**, *32*, 1304; Paquette, L. A.; Williams, R. V. *Tetrahedron Lett.* **1981**, 4643) and 1,5-cyclooctadiene (Eaton, P. E.; Chakraborty, U. R. *J. Am. Chem. Soc.* **1978**, *100*, 3634) are examples of cyclic alkenes that cycloadd to highly reactive dienes.

[2] (a) Carr, R. V. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1980**, *102*, 853. (b) Paquette, L. A.; Kinney, W. A. *Tetrahedron Lett.* **1982**, 131. (c) Little, R. D.; Myong, S. O. *Ibid.* **1980**, 3339. (d) Paquette, L. A.; Charumilind, P. *J. Am. Chem. Soc.* **1982**, *104*, 3749. (e) Paquette, L. A.; Williams, R. V.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *J. Org. Chem.*, **1982**, *47*, 4566.

[3] For previous examples of sulfone activation of olefins, see: (a) Böll, W.; König, H. *Justus Liebigs Ann. Chem.* **1979**, 1657. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429. (c) Danishefsky, S.; Marayama, T.; Singh, R. K. *Ibid.* **1979**, *101*, 7008.

[4] Consult, for example: (a) Vig, O. P.; Kapoor, J. C.; Puri, J.; Sharma, S. D. *Ind. J. Chem.* **1980**, *6*, 60. (b) Kelly, L. F.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1980**, 2455. (c) Escalona, H.; Maldonado, L. A. *Synth. Commun.* **1980**, *10*, 857. (d) Kelly, L. F.; Dahler, P.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1981**, 1433.

[5] Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, 2213.

[6] Gancarz, R. A.; Kice, J. L. *Tetrahedron Lett.* **1980**, 4155; *J. Org. Chem.* **1981**, *46*, 4899. This photochemical procedure proved to be more efficient in our hands than the thermal alternative [Back, T. G.; Collins, S. *Tetrahedron Lett.* **1980**, 2215; *J. Org. Chem.* **1981**, *46*, 3249].

[7] The yields cited herein apply to purified products that were homogeneous by TLC analysis and gave elemental analyses and spectral data (^{1}H NMR, IR, *m/e*) in accord with their assigned structures.

[8] Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

[9] Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602.