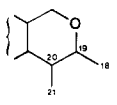
Table II. ^{1}H NMR Data of 1-4[a]

	1	2	3		1	2	4
H-3′	4.02	4.05 br t (2)	3.95 br t	H-3	3.93	3.93 dd	3.60 (d)-2.92 (d)
H-5′	3.10 d	3.19 d (7)	2.92 d	H-5α	2.86 dd	2.84 dd (10, 6.5)	3.02 m
H-6′α	3.30 dd	3.38 dd (17.5, 7)	3.26 dd	H-5β	2.79 ddd	2.54 ddd (10, 11, 5)	2.70 m
H-6′β	2.56 d	2.68 d (17.5)	2.47 d	H-6α	2.00 dt	2.00 dt (11, 11, 6.5)	2.10 dt
H-9′	7.40 br d	7.48 br d (7)	-	H-6β	1.65	1.62 dd (11, 5)	1.72 dd
H-10′	6.95 br t	7.02 br t (7)	-	H-9	6.34 s	5.63 s	-
H-11′	7.06 br t	7.13 br t (7)	-	H-14	3.09 br d	3.15 dd (3, 1)	3.28 br d
H-12′	7.32 br d	7.24 br d (7)		H-15	3.02 d	3.07 d (3)	3.06 d
H-13′	1.67		2.40 m	H-17α	2.58 br d	2.91 br d (16.5)	2.70 d
H-14′	2.15	2.10-2.20 m	1.46 br d	H-17β	2.40 d	2.73 d (16.5)	2.52 d
H-15′	2.20		2.22 m	H-18	0.69 m	0.81 m	0.72 t
H-16′	2.11		2.06 m	H-19	0.82 m		0.98 m
H-17′α	4.40 t	4.50 t (11)	4.12 t	H-21	2.50 s	2.30 br s	2.42 s
H-17′β	4.00 dd	4.10 dd (11, 3.5)	3.92 dd	OCH_3	3.71 s	3.93 s	-
H-18′	5.05 dd	5.06 dd (16, 8)	-		3.87 s	4.08 s	-
H-19′	5.85 d	6.02 d (16)	-		3.89 s	4.27 s	-
H-21′	6.41 s	6.56 s	-				
N(1′)CH_3	3.62 s	3.65 s	3.64 s				
N(4′)CH_3	2.39 s	2.39 s	2.30 s				

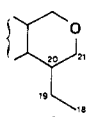
[a] $CDCl_3$, Me_4Si = 0 ppm, s = singlet, d = doublet, t = triplet, m = multiplet. Numbers in parentheses are the coupling constants J (hertz). For clarity the J values for 1, 3, and 4 are omitted, but they are roughly equal to the corresponding values observed for 2.

tween C(20′) and C(21′), the latter carbon being linked to an oxygen as evident from its chemical shift: C(21′) at 145.7 ppm and H(21′) at 6.41 ppm.

Of the two biogenetically possible arrangements, 5 and 6, of the C(18′) → C(21′) chain linkage of the macroline moiety, only the latter (6) can accommodate the above-mentioned facts.

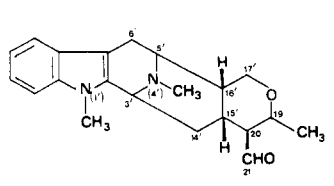


5

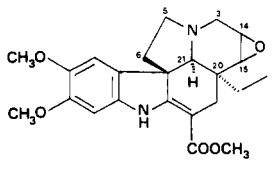


6

The same conclusions could be reached from a close examination of the 240-MHz ^{1}H NMR spectra[11] (Table II) of 1 and 2. Thus, irradiation of H(18′) at 5.06 ppm in the spectrum of 1 transformed the H(3) at 3.93 ppm into a doublet (J = 1 Hz), which is coupled in turn to the AB system formed by H(14) and H(15) [δ 3.15 (dd, J = 3, 1 Hz), 3.07 (d, J = 3 Hz)]. These results were obtained by direct irradiation, but H(3), which is hidden in the congested methoxyl proton region, could be recognized by using the difference spectroscopy technique.[12] This procedure allowed identification of all the 48 protons in 2 and it was interesting to note that in the nonaromatic region the spectrum was almost a superimposition of the spectra of the two monoindole alkaloids talcarpine[13] (7) and hazuntinine[14] (8), most of the protons having the same shapes and the same chemical shifts.



7



8

(11) We are grateful to Drs. S. K. Kan and P. Gonord for 240-MHz ^{1}H NMR spectra.

(12) G. Massiot, S. K. Kan, P. Gonord, and C. Duret, *J. Am. Chem. Soc.*, **97**, 3227 (1975).

(13) J. Naranjo, M. Pinar, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, **55**, 752 (1972).

(14) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Am. Chem. Soc.*, **95**, 4990 (1973).

The above results lead us to propose structure 1 for pandicine with the depicted stereochemistry. Although we have no proof for the relative stereochemistry of the two moieties present in pandicine (1), it seems reasonable to assume that they have the natural configurations of talcarpine (7) and hazuntinine (8).

The highly substituted aromatic ring of the tabersonine moiety and a modified macroline unit in the form of anhydromacrosalhine[10] are the novel features of the structure of pandicine (1).

Registry No. 1, 76282-39-8; 2, 76282-40-1; 3, 52659-53-7; 4, 2723-56-0.

Dienophilic Reactions of 3-[(Trimethylsilyl)oxy]-3-buten-2-one

Robert J. Ardecky, Francis A. J. Kerdesky, and Michael P. Cava*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received June 12, 1980

The monoenol derivatives of the inexpensive diketone biacetyl are α-oxygenated analogues of methyl vinyl ketone, and as such they should be synthetically useful dienophiles in [4 + 2] addition reactions. The first example of such a reaction was reported in 1966, using 3-acetoxy-3-buten-2-one.[1] Since the preparation of the latter from biacetyl afforded a low yield after a tedious purification,[1] we decided to examine the dienophilic properties of 3-[(trimethylsilyl)oxy]-3-buten-2-one (1, TBO), the readily prepared mono(trimethylsilyl) derivative of biacetyl.[2,3] The only Diels–Alder reactions of TBO hitherto reported are its thermal dimerization and its addition to the bis(trimethylsilyl) derivative of biacetyl.[3]

We have studied the reaction of a series of representative dienes with excess TBO. The initial adducts were not

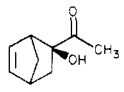
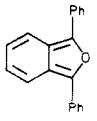
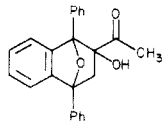
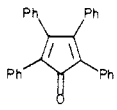
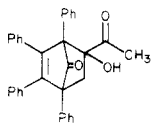
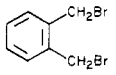
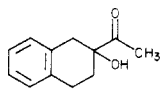
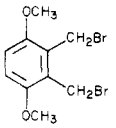
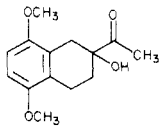
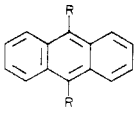
(1) Wharton, P. S.; Aw, B. T. *J. Org. Chem.* **1966**, **31**, 3789.

(2) Barnier, J. P.; Garnier, B.; Girard, C.; Denis, J. M.; Salaun, J.; Conia, J. M. *Tetrahedron Lett.* **1973**, 1747.

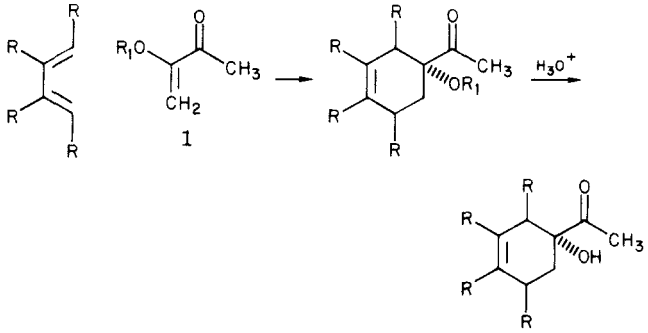
(3) Murai, S.; Ryu, I.; Kadono, Y.; Katayama, H.; Kondo, K.; Sonoda, N. *Chem. Lett.* **1977**, 1219.

0022-3263/81/1946-1483$01.25/0

Table I. α-Ketols from TBO

diene or precursor	desilylated adduct	% yield
	 4	44
	 5	54
	 6	52
 2	 7	26
 3	 8	18
 R = H or R = CH_3	none	0

isolated but were desilylated directly with acetic acid to afford the corresponding α-ketols as shown below. The individual dienes or diene precursors used, and the α-ketols isolated are listed in Table I.



R_1 = $SiMe_3$

The dienophilic activity of TBO proved to be only fair. While cyclopentadiene and 1,3-diphenylisobenzofuran reacted under mild conditions, the reaction with tetraphenylcyclopentadienone required a number of hours in refluxing toluene. Both anthracene and 9,10-dimethylanthracene failed to add to TBO, even after heating for several days in refluxing toluene.

The trapping of several *o*-quinodimethanes by TBO could also be achieved, albeit in modest yield. Thus, reaction of α,α′-dibromo-*o*-xylene (**2**) or its 3,6-dimethoxy derivative **3** with zinc dust in the presence of TBO, followed by acid desilylation, afforded the known tetralin ketols **7** and **8** in yields of 26% and 18%, respectively. It should be noted that ketol **8** is a key intermediate in several syntheses of the currently important anthracycline anticancer antibiotics.[4]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared (KBr) and mass spectra were determined by using Perkin-Elmer 137 and 270B spectrometers, respectively. NMR spectra were recorded in $CDCl_3$ solutions containing Me_4Si as internal standard and are reported in δ units; Varian A-60A and Brucker 250-MHz instruments were employed. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Activated zinc was prepared by stirring zinc dust with saturated aqueous NH_4Cl and subsequently washing with methanol, ether, and DMF.

3-(Trimethylsiloxy)-2-buten-2-one. The procedure used for preparation of TBO was essentially that of Murai[3] except methylene chloride was used as a solvent and a Kugelrohr apparatus was used for distillation.

5-Acetyl-5-hydroxybicyclo[2.2.1]hept-2-ene.[5] A mixture of 500 mg of freshly distilled cyclopentadiene and 500 mg of 3-(trimethylsiloxy)-3-buten-2-one was stirred for 2 h at −78 °C and warmed to room temperature. Hydrolysis with HOAc/THF/H_2O (3:2:2) at 45 °C for 2 h and subsequent evaporation gave an oily residue. The residue was chromatographed (SiO_2, C_6H_6) and recrystallized from benzene–hexane to give colorless needles: mp 80–82 °C (0.21g, 42%); NMR 1.20 (s, 3 H, $COCH_3$), 2.0–2.8 (m, 6 H, aliphatic), 4.25 (s, 1 H, OH), 5.95 (q, 2 H, vinyl), 6.20 (q, 2 H, vinyl); IR 3550 (OH), 1720 (C=O); mass spectrum,). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.33; H, 7.81.

5-Acetyl-5-hydroxy-1,2,3,4-tetraphenyl-2-norbornen-2-one.[5] Tetraphenylcyclopentadienone (190 mg, 0.5 mol) was dissolved in toluene (50 mL). 3-(Trimethylsiloxy)-3-buten-2-one (200 mg) dissolved in toluene (5 mL) was added to the cyclone solution by drops.

After the mixture was refluxed for 12 h, hydrolysis with HOAc/THF/H_2O (3:2:2) and removal of the solvent (Buchi) gave a solid. Chromatography (SiO_2, C_6H_6) followed by recrystallization from methanol afforded colorless crystals: mp 209–211 °C (122 mg, 52%); NMR 1.52 (s, 3 H, $COCH_3$), 3.61 (s, 1 H, OH), 6.70–7.58 (m, 20 H, aromatic); IR 3380 (OH), 1745 (C=O), 1705 (C=O), 1600 (aromatic); mass spectrum, *m/e* 470 (M^+), 452 (M − H_2O). Anal. Calcd for $C_{33}H_{26}O_3$: C, 84.26; H, 5.53. Found: C, 84.56; H, 5.49.

1,4-Diphenyl-1,4-epoxy-2-acetyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene.[5] Diphenylisobenzofuran (135 mg, 0.5 mmol) was dissolved in dry methylene chloride (35 mL). 3-(Trimethylsiloxy)-3-buten-2-one (200 mg) in 3 mL of methylene chloride was added by drops to the solution. The reaction mixture was refluxed for 12 h. Hydrolysis with HOAc/THF/H_2O (3:2:2) and removal of the solvent (Buchi) gave a solid residue. Chromatography (SiO_2; C_6H_6) and recrystallization from methanol gave colorless crystals: mp 118–119 °C (96 mg, 54%); NMR 1.55 (s, 3 H, $COCH_3$), 3.50 (s, 1 H, OH), 7.18–8.30 (m, 14 H, aromatic); IR 3400 (OH), 1715 (C=O), 1600 (aromatic); mass spectrum, *m/e* 356 (M^+), 313 (M − $COCH_3$). Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.90; H, 5.62. Found: C, 80.91; H, 5.64.

2-Acetyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene. α,α′-Dibromo-*o*-xylene (132 mg, 0.5 mmol) was dissolved in 5 mL of dry DMF. This solution was added by drops to a stirred suspension of 3-(trimethylsiloxy)-3-buten-2-one (2.0 g), hydroquinone (10 mg), DMF (5 mL), and activated zinc dust (1.0 g). The mixture was stirred for 15 min. After the zinc was filtered off, the organic layer was acidified with HOAc and heated to 45 °C for 2 h. The

(4) (a) Wong, C. M.; Popien, D.; Schwenk, R.; Te Raa, J. *Can. J. Chem.* **1971**, *49*, 2712. (b) Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Su, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653. (c) Arcamone, F.; Bernard, L.; Giardino, P.; Patelli, B.; DiMarco, A.; Casazza, A. M.; Pratesi, G.; Reggiani, P. *Cancer Treat. Rep.* **1976**, *60*, 829. (d) Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T. L. *Can. J. Chem.* **1973**, *51*, 466. (e) DiMarco, A.; Casazza, A. M.; Giuliano, P.; Pratesi, G.; Arcamone, F.; Bernardi, L.; Franchi, G.; Giardino, P.; Patelli, B.; Penco, S. *Cancer Treat. Rep.* **1978**, *62*, 375. (f) Kende, A. S.; Curran, D. P.; Tsay, Y. G.; Mills, J. E. *Tetrahedron* **1977**, 3537. Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G. *Tetrahedron Lett.* **1978**, 3765. (h) Arcamone, F.; Bernardi, L.; Patelli, B.; Giardino, P.; DiMarco, A.; Casazza, A. M.; Soranzo, C.; Pratesi, G. *Experientia* **1978**, *34*, 1255.

(5) This compound may be assumed to have the expected endo conformation, although this point has not been proven.

mixture was poured into water and extracted with CH_2Cl_2. The layers were separated and the CH_2Cl_2 layer was dried over sodium sulfate. Chromatography (SiO_2; hexane–ether) gave a colorless oil: 31 mg (26%); NMR 1.90 (m, 2 H, CH_2), 2.33 (s, 4 H, $COCH_3$), 2.90 (m, 4 H, benzylic), 7.20 (s, 4 H, aromatic); IR 3525 (6 H), 1710 (c=O), 1600 (aromatic); mass spectrum, *m/e* 190 (M^+), 147 (M – $COCH_3$).

This compound was further identified by the preparation of its semicarbazone. 2-Acetyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene (30 mg, 0.16 mmol) was added to a mixture of semicarbazide hydrochloride (150 mg, 1.05 mmol) and sodium acetate (50 mg) in a solution of 10 mL of EtOH and 5 mL of H_2O. after being heated for 1 min, the solution was then cooled to 0 °C. The semicarbazone crystallized out of solution. Recrystallization from acetic acid gave colorless crystals; mp 220–222 °C (lit.[6] mp 221–223 °C) (18 mg, 72%).

2,3-Bis(bromomethyl)-1,4-dimethoxybenzene. 2,3-Dimethyl-1,4-dimethoxy-benzene (166 mg, 1 mmol) and *N*-bromosuccinimide (445 mg, 2.5 mmol) were dissolved in dry carbon tetrachloride (150 mL) containing benzoyl peroxide (25 mg). The solution refluxed for 24 h. After the mixture cooled, the succinimide was filtered and the filtrate evaporated. The residue was washed with dilute base and then water and dried. Chromatography (SiO_2, C_6H_6) and recrystallization from petroleum ether gave colorless crystals: mp 147–149 °C (lit.[7] mp 149 °C) (264 mg, 81%); NMR 3.85 (s, 6 H, 2 OCH_3), 4.61 (s, 4 H, 2 CH_2Br), 6.70 (s, 2 H, aromatic).

2-Acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene. 2,3-Bis(bromomethyl)-1,4-dimethoxybenzene (160 mg, 0.5 mmol) was added portionwise to a stirred suspension of 3-(trimethylsiloxy)-3-buten-2-one (2.0 g), hydroquinone (10 mg), activated zinc dust (1.0 g), and 10 mL of dry DMF. After the mixture was stirred for 30 min, the zinc was filtered. The organic layer was then acidified with HOAc and heated to 45 °C for 2 h. The solution was poured into H_2O and filtered. The residued was chromatographed (SiO_2, C_6H_6). Recrystallization from petroleum ether gave colorless crystals: mp 96–97 °C (lit.[4b] mp 97 °C) (23 mg, 17%); NMR 1.90 (m, 2 H, CH_2), 2.33 (s, 3 H, $COCH_3$), 2.90 (m, 5 H, benzylic and OH), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.66 (s, 2 H, aromatic); IR 3525 (OH), 1705 (C=O), 1600 (aromatic); mass spectrum, *m/e* 250 (M^+), 207 (M – $COCH_3$).

Acknowledgment. This investigation was supported by a grant, CA-24199, awarded by the National Institutes of Health.

Registry No. 1, 42082-94-0; 2, 91-13-4; 3, 19164-83-1; 4, 76376-98-2; 5, 76376-99-3; 6, 76377-00-9; 7, 76377-01-0; 7 semicarbazone, 76377-02-1; 8, 71366-25-1; cyclopentadiene, 542-92-7; diphenylisobenzofuran, 5471-63-6; tetraphenylcyclopentadienone, 479-33-4; 2,3-dimethyl-1,4-dimethoxybenzene, 39021-83-5; anthracene, 120-12-7; 9,10-dimethylanthracene, 781-43-1.

(6) Terashima, S.; Jew, S. S.; Koya, K. *Tetrahedron Lett.* **1977**, 4507.
(7) McHale, D.; Mamalis, P.; Marcinkienicz, S.; Green, G. *J. Chem. Soc.* **1959**, 3358.

Ortho Ester Claisen Rearrangements Using Trimethyl Methoxyorthoacetate

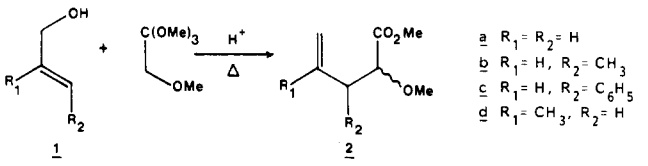
G. William Daub,* Douglas H. Teramura, Kevin E. Bryant, and Mark T. Burch

Department of Chemistry, Harvey Mudd College, Claremont, California 91711

Received September 10, 1980

During the past 10 years the Claisen rearrangement has been developed into a very general and powerful synthetic tool.[1] In particular, enolate Claisen methods[2] and ortho ester/ketal exchange procedures[3] have provided the synthetic chemist with convenient new methods for exploiting this historically important pathway to γ,δ-unsaturated carbonyl compounds.

Scheme I



The generality of these methods has typically been demonstrated by substituting the basic allyl vinyl ether framework with alkyl or aryl groups. Only in a few cases has a heteroatom been included as a substituent.[2,4-8] Ireland[2,8] and Still[5] have previously demonstrated that heteroatom substitution is compatible with the enolate Claisen reaction, which proceeds under basic conditions. Recent efforts in our laboratory have centered around the use of an α-methoxy ortho ester in the ortho ester Claisen rearrangement, a process that occurs under acidic conditions.

Trimethyl methoxyorthoacetate[9] participates as the ortho ester partner in the Claisen rearrangement (Scheme I), producing α-methoxy γ,δ-unsaturated methyl esters in fair yields (20–55%). The allylic alcohol 1 was heated (100–125 °C) with 2 equiv of trimethyl methoxyorthoacetate in the presence of a weak acid for 18 h at ambient pressure (method A) or in a sealed tube (method B). Shorter or longer reaction times did not appear to be beneficial. Gas chromatography indicated that the crude reaction mixture usually contained >10 components, with the desired product predominating. Subsequent chromatography on silica gel afforded the α-methoxy esters **2**.

The α-methoxy esters (**2**) were characterized by spectroscopic (IR, ^1H NMR, mass spectra) and chromatographic (TLC, VPC) methods. In cases where diastereomeric mixtures were expected (**2b**, **2c**), careful ^1H NMR analysis confirmed the presence of a ca. 1:1 mixture of the threo and erythro isomers. In particular, the methoxy and carbomethoxy protons in **2c** exhibited different chemical shifts (Δ = 3.0 Hz), while the methyl doublets in **2b** showed a somewhat smaller chemical shift difference (Δ = 1.2 Hz). We attribute the larger observed chemical shift difference in **2c** to the presence of the strong anisotropic effects of the aromatic ring. These diastereomeric mixtures proved inseparable by chromatography (TLC, VPC).

A reaction attempted between trimethyl methoxyorthoacetate and cyclohex-2-en-1-ol afforded no material that was consistent with the anticipated α-methoxy ester. Thus, the competing elimination reactions inherent in the ortho ester modification of the Claisen rearrangement render this method ineffective as well.[1b]

(1) (a) G. B. Bennett, *Synthesis*, 589 (1977); (b) F. E. Zeigler, *Acc. Chem. Res.*, **10**, 227 (1977).
(2) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
(3) W. S. Johnson, L. Werthemann, W. R. Bartlett, J. J. Brocksom, T. Lee, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.*, **92**, 741 (1970).
(4) L. Werthemann and W. S. Johnson, *Proc. Natl. Acad. Sci. U.S.A.*, **67**, 1465 (1970).
(5) W. C. Still and M. J. Schneider, *J. Am. Chem. Soc.*, **99**, 950 (1977).
(6) S. Rauscher, K.-J. Hwang, and J. E. McDonald, *Tetrahedron Lett.*, 3057 (1979).
(7) S. Rauscher, J. E. Macdonald, and R. F. Lawrence, *Tetrahedron Lett.*, 4335 (1980).
(8) R. E. Ireland, S. Thaisrivongs, N. Vanier, and C. S. Wilcox, *J. Org. Chem.*, **45**, 48 (1980).
(9) J. H. van Boom, G. R. Owen, J. Preston, T. Ravindranathan, and C. B. Reese, *J. Chem. Soc. C*, 3230 (1971).

0022-3263/81/1946-1485$01.25/0