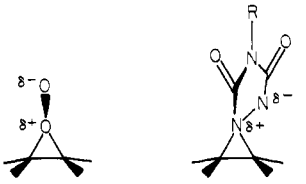
Table I. Isotope Effects in the Reaction of C_6F_5NO and Tetramethylethylene (3)

olefin	k_H/k_D
(Z)-3[a]	1.2 ± 0.2
(E)-3[a]	3.0 ± 0.2
gem-3[a]	4.5 ± 0.2
3-d_0, 3-d_{12}[b]	1.03 ± 0.05

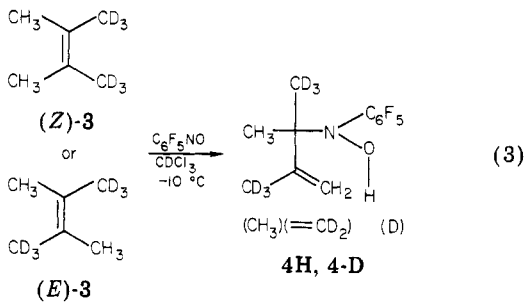
[a] In $CDCl_3$, see footnote 11a. [b] In Et_2O, see footnote 11b.

proceed through intermediates, most simply interpreted (in our opinion) as three-center species (e.g., 1 and 2).[8] It



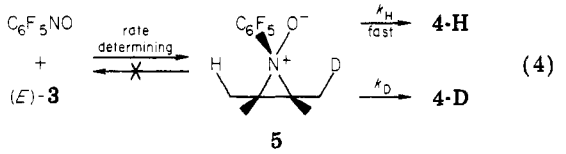
1 2

is of interest to ascertain how broadly intermediates (and specifically, three-center species) may be involved in reactions of olefins with various reagents. We have applied the Stephenson isotope test[6a] [use of (Z)- and (E)-2,3-bis(trideuteriomethyl)-2-butene, 3] to the reaction of nitrosopentafluorobenzene,[9] and have also determined the intramolecular isotope effect with tetramethyl-gem-d_6-ethylene [$(CH_3)_2C{=}C(CD_3)_2$, gem-3][10] and the intermolecular isotope effect (by competition with tetramethylethylene-d_0 and -d_{12}).[11] The results are summarized in eq 3 and Table I.



(Z)-3 or (E)-3 → 4H, 4-D (3)

The lack of an intermolecular isotope effect compared with large isotope effects with (E)-3 and gem-3, and the substantial difference in isotope effects for (E)-3 compared to (Z)-3, are strong evidence against a mechanism (e.g., eq 2) involving cleavage of an allylic carbon–protium bond in the rate-determining step. The results are consistent with rate-determining formation of an intermediate, followed by cleavage of the "allylic" carbon–protium bond in a subsequent (and faster) step—with isotopic discrimination when "allylic" C–H is cis to C–D (i.e., in (E)-3 and in gem-3).[12] These results (eq 3 and Table I) are accommodated by an aziridine N-oxide, e.g., 5 (eq 4).



(E)-3 → 4-H, 4-D (4)

5

Aziridine N-oxides[13] are strongly implicated in the ozonolysis of aziridines; species considered to be aziridine N-oxides (considerably less hindered than 5 in eq 4) were observed directly by NMR at low temperatures and decomposed to unsaturated hydroxylamines (analogous to 4) and to nitrosoalkanes and olefins.[13a]

In summary, nitroso compounds, singlet oxygen, and triazolinediones appear to react with simple olefins via rate-determining formation of intermediates—5, 1, and 2 or species with these structural characteristics.

Registry No. 3-d_0, 563-79-1; (E)-3, 38132-24-0; (Z)-3, 38132-19-3; gem-3, 38132-23-9; 3-d_{12}, 69165-86-2; 4H, 30287-20-8; C_6H_5NO, 1423-13-8; D_2, 7782-39-0.

(8) For some evidence on mechanisms of ene reactions, including temperature dependence of isotope effects, see Munsterer, H.; Kresze, G.; Brechbiel, M. W.; Kwart, H. *J. Org. Chem.* **1982**, *47*, 2677, and Kwart, H.; Brechbiel, M. W. *Ibid.* **1982**, *47*, 3353.

(9) Compound 4, undeuterated, N-(1,1,2-trimethyl-2-propenylpentafluorophenyl)hydroxylamine (ref 3a), mp 78–79 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (t, J = 1.6 Hz, 6 H), 1.92 (s, 3 H), 4.96 (s, 1 H), 5.02 (br s, 1 H), 5.20 (br, 1 H, OH).

(10) We thank Chen-Chih Cheng for the tetramethyl-gem-d_6-ethylene.

(11) (a) Intramolecular isotope effects were determined in $CDCl_3$ by ^1H NMR analysis of products (see footnote 9). (b) Intermolecular isotope effects were determined in diethyl ether by GC–mass spectral analysis for tetramethylethylene at time = 0 (before the addition of C_6F_5NO) and at time = ∞ (2 h) starting with a 1:1:1 ratio of TME-d_0, TME-d_{12}, and C_6F_5NO, initial concentrations 0.005 M.

(12) The larger isotope effect observed with gem-3 (4.5) compared with (E)-3 (3.0), also seen in the reactions of these olefins with singlet oxygen (ref 6b) and with N-phenyl- and N-methyltriazolinedione (unpublished results of these laboratories), probably arises from secondary β-D isotope effects on the developing double bonds in the transition states for H (and D) transfer.

(13) (a) Baldwin, J. E.; Bhatnagar, A. K.; Choi, S. C.; Shortridge, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 4082. (b) Aziridine N-oxides also have been suggested as intermediates in the enzymatic oxidation of aziridines: Hata, Y.; Watanabe, M.; Matsubara, T.; Touchi, A. *J. Am. Chem. Soc.* **1976**, *98*, 6033. See also Hata, Y.; Watanabe, M. *Ibid.* **1979**, *101*, 1323.

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Conjugate Addition of RMgX to Mononitroarenes. Unequivocal Evidence for a Single-Electron-Transfer Mechanism

Summary: 1,6 conjugate addition of 5-hexenylmagnesium bromide to 2-methoxy-1-nitronaphthalene in THF at room temperature provides an unequivocal evidence for a single-electron-transfer pathway of the reaction, resulting in a 36% of cyclized vs. a 64% of uncyclized product.

Sir: Conjugate addition of RMgX to mononitroarenes[1] and its synthetic application[2] has been reported by us in recent years. So far it has not been strictly examined if this reaction proceeds exclusively through a polar mechanism or rather, as already well-recognized for related reaction of Grignard reagents with aromatic ketones,[3] a single-electron-transfer (SET) pathway could be involved as well.

Recently Savin,[4] using ESR and CIDNP techniques, observed the formation of nitrobenzene radical anion and

(1) (a) G. Bartoli, R. Leardini, A. Medici, and G. Rosini, *J. Chem. Soc., Perkin Trans. 2*, 692 (1978); (b) G. Bartoli, M. Bosco, A. Melandri, and A. C. Boicelli, *J. Org. Chem.*, **44**, 2087 (1979).

(2) (a) G. Bartoli, A. Medici, G. Rosini, and D. Tavernari, *Synthesis*, 436 (1978); (b) G. Bartoli and M. Bosco, *Synthesis*, 616 (1980); (c) G. Bartoli, M. Bosco, and G. Baccolini, *J. Org. Chem.*, **45**, 522 (1980).

(3) E. C. Ashby and J. R. Bowers, Jr., *J. Am. Chem. Soc.*, **103**, 2242 (1981).

(4) V. I. Savin, *Zh. Org. Chim.*, 14, 2090 (1978); *Chem. Abstr.*, **90**, 71443r (1979).

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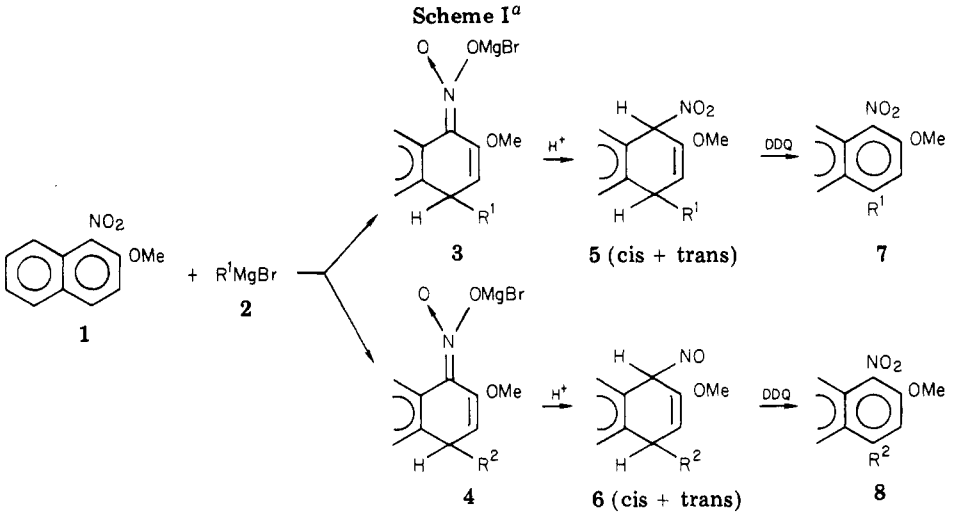
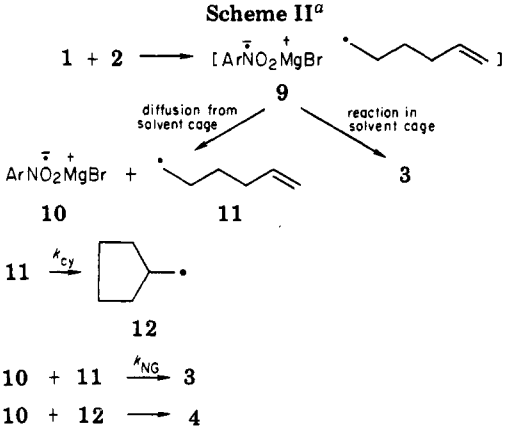
Scheme I[a]



[a] R^1 = 5-hexenyl, R^2 = cyclopentylmethyl.

tert-butyl radical during the reaction between nitrobenzene and *tert*-butylmagnesium chloride, leading to N-alkylation (36%) and ring alkylation (28%) products. Such spectroscopic results were considered to suggest a SET mechanism, as reaction products might originate from collapse of radical intermediates. In order to verify the occurrence of a SET mechanism in systems[1] where ring alkylation does actually constitute the major process, we chose a different approach that would hopfully provide a more straightforward argument on this concern. Thus we incorporated a radical probe in the R group of the Grignard reagent. The 5-hexenyl derivative proved to be a useful tool in this direction,[5] since 5-hexenyl radical undergoes rapid cyclization[6] predominantly to cyclopentylmethyl radical. Hence, if the alkyl transfer from organometallic to aromatic substrate takes place with radical character, products containing cyclopentylmethyl group are likely to be obtained. Therefore, 10 mmol of 5-hexenylmagnesium bromide[7] in 50 mL of THF, freshly prepared in conditions in which formation of cyclic isomer is negligible[8] (<3%), were allowed to react with 2-methoxy-1-nitronaphthalene (5 mmol) in the same solvent, at room temperature for a few minutes, and then quenched with aqueous acetic acid (3%) (Scheme I). After usual work up, the reaction mixture was submitted to a preliminary ^{1}H NMR analysis, from which the presence of cis and trans derivatives **5** (uncyclized) and **6** (cyclized) could be detected. However, owing to the complexity of the spectrum, it was impossible to establish the relative proportions between **5** and **6**. Thus the crude dihydro isomers were oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at reflux in dry benzene.[9] The usual workup gave a mixture of 4-(5-hexenyl)-2-methoxy-1-nitronaphthalene (**7**) and 4-(cyclopentylmethyl)-2-methoxy-1-nitronaphthalene (**8**) in 78% of total yield. ^{1}H NMR[10] analysis gave the following

Scheme II[a]



[a] Ar = 4-methoxynaphthyl.

proportions: 64% of **7** and 36% of **8**. Separation of the two isomers was performed by submitting a sample of 0.3 g of the purified material to high-perssure chromatography on a Cromatospac Ivon Jobin prep column (eluent: benzene–cyclohexane, 3:2). **7** (0.17 g, 63%; mp 41–43 °C) and 0.11 g (37%) of **8** (mp 72–73 °C) were obtained with a loss of about 10%.

The present results show that at least 36% of 1,6 conjugate addition of **2** to **1** proceeds through a SET pathway.

However, it seems very reasonable to assume an analogous mechanism for formation of uncyclized product.

A single electron transfer occurs from **2** to **1** to give the radical pair **9** (Scheme II). The alkyl radical can migrate from the region in which it is formed (near the nitro group) to the para position of the nitroarene radical anion and then collapse at this position in a geminate recombination,[11] or escape the solvent cage. Very likely, geminate recombination gives exclusively uncyclized product **3**. In fact, if the lifetime of the radical pair is governed by diffusion coefficient of usual magnitude, the cage reaction must be complete within $\sim 10^{-9}$ s[-1] [12] and therefore cyclization ($k_{cy} \simeq 10^5$ s^{-1})[6] cannot compete with geminate recombination or cage escape. Thus, cyclization can only

(5) (a) C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, **92**, 6609 (1970); (b) *ibid.*, **94**, 6059 (1972); (c) E. C. Ashby and J. S. Bowers, Jr., *ibid.*, **99**, 8504 (1977).

(6) D. Lal, D. Griller, S. Husband, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 6355 (1974).

(7) Commercial 99.99% magnesium chips (m4N, Pierce and Warriner LTD.) were used without any activation.

(8) The Grignard reagent was carbonated with freshly crushed dry ice and the composition of the isomers detected by analysis of resulting carboxylic acids; cf. also R. C. Lamb, P. W. Ayers, M. K. Toney, and J. F. Garst, *J. Am. Chem. Soc.*, **88**, 4261 (1966).

(9) It was checked that DDQ does not provoke cyclization of the bonded hexenyl group. In fact, product **7**, kept at reflux in dry benzene for a day with DDQ, was recovered unaltered.

(10) ^{1}H NMR ($CDCl_3$, ppm from Me_4Si) spectra data follow. **7**: 1.44–2.30 (m, 6 H), 3.10 (t, CH_2, J = 7.0 Hz), 4.02 (s, OMe), 4.94–5.10 and 5.64–6.06 (m, H_2C=CH), 7.18 (s, H_3), 7.40–8.12 (m, 4 H). **8**: 1.00–2.46 (m, 9 H), 3.10 (d, CH_2, J = 7.0 Hz), 4.02 (S, OMe), 7.16 (s, H_3), 7.36–8.10 (m, 4 H). All compounds gave satisfactory microanalyses.

(11) J. F. Garst and C. D. Smith, *J. Am. Chem. Soc.*, **98**, 1526 (1976).

(12) R. M. Noyes, *J. Am. Chem. Soc.*, **77**, 2042 (1955).

occur in radicals that have escaped their geminate original partners.

Otherwise free alkyl radicals **11** can collapse with **10** in a nongeminate recombination[11] or cyclize to cyclopentylmethyl radicals **12**. Collapsing of **12** with **10** gives adduct **4**. The ratio of products **3** and **4**, originated by nongeminate recombination is governed by the following equation: $d[3]/d[4] = k_{NG}[10]/k_{cy}$ where k_{NG} is the rate constant for collapsing of **11** with **10**. k_{NG} has been estimated to be $\sim 10^8$ M^{-1} s^{-1} for coupling between ketyls and 5-hexenyl radicals,[13] and a close value can be reasonably assumed for the more stable nitro radical anion **10**.[14] On this basis a steady-state concentration of **10** $< 10^{-3}$ M is sufficient to allow most radicals that escape the geminate recombination to cyclize before recombining with **10**.

Registry No. 1, 4900-66-7; 2, 30043-41-5; *cis*-5, 83693-44-1; *trans*-5, 83693-45-2; *cis*-6, 83693-46-3; *trans*-6, 83693-47-4; 7, 83693-48-5; 8, 83693-49-6.

(13) J. F. Garst and C. D. Smith, *J. Am. Chem. Soc.*, **98**, 1520 (1976).
(14) E. G. Janzen, *Acc. Chem. Res.*, **2**, 279 (1969).

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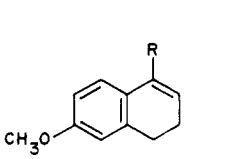
A Synthesis of (±)-Estrone Methyl Ether via the Tandem Cope–Claisen Rearrangement

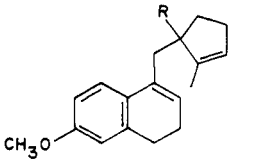
Summary: A synthesis of (±)-estrone methyl ether (**7b**) is described that employs a new approach to the construction of the estrogen skeleton invoking the tandem Cope–Claisen rearrangement.

Sir: Estrogens continue to attract attention as synthetic targets because their well-defined structures provide an opportunity to test new reactions and explore their stereochemistry. We have defined and explored the utility of the tandem Cope–Claisen rearrangement[1] and have applied it to a novel synthesis of (±)-estrone methyl ether (**7b**).[2,3]

Bromide **1b** (mp 57.5–58 °C) was prepared[4] in 68% overall yield by sequential reduction ($LiAlH_4$, Et_2O, 0 °C), mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C), and displacement (LiBr, acetone, reflux) of aldehyde **1a**.[2] The anion of methyl 2-methyl-2-cyclopentene-1-carboxylate[5] (LDA, THF, −70 °C) was alkylated with bromide **1b** to afford ester **2a** in 94% yield.[6] Subsequent reduction of the ester ($LiAlH_4$, Et_2O, 0 °C) gave rise to alcohol **2b** (93% yield), which was vinylated ($Hg(OAc)_2$, CH_2=CHOEt, reflux) to provide vinyl ether **2c** (94% yield).

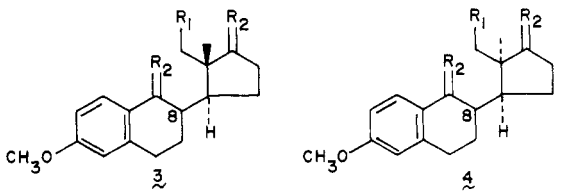


1a, R = CHO
b, R = CH_2Br



2a, R = CO_2CH_3
b, R = CH_2OH
c, R = CH_2OCH=CH_2

Thermolysis of vinyl ether **2c** (370 °C, 20 s, evacuated ampule) afforded a 2/1 mixture (60% yield) of diastereomeric aldehydes. The major component, isolated in 35% yield, was shown by single-crystal X-ray analysis to be aldehyde **3a**.[7] The structure of the minor isomer was proved to be aldehyde **4a** by the following method. Sequential exposure of aldehyde **3a** to $LiAlH_4$, Ac_2O/pyr, and



3

4

a, R_1 = CHO, R_2 = CH_2, C_8-αH
b, R_1 = CHO, R_2 = O, C_8-αH
c, R_1 = CHO, R_2 = O, C_8-βH

(1) (a) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611. (b) *Ibid.* **1980**, *102*, 880. (c) *Ibid.* **1980**, *102*, 6576. (d) Raucher, S.; Burks, J. E., Jr.; Hwang, K.-J.; Svedberg, D. P. *Ibid.* **1981**, *103*, 1853.
(2) For recent pertinent references for the synthesis of estrogens, see Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1981**, 1179.
(3) (a) Quinkert, G.; Weber, W. D.; Schwartz, U.; Duerner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1027. (b) Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Baier, H.; Adam, F.; Duerner, G. *Ibid.* **1980**, *19*, 1029. (c) Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921.
(4) All new compounds gave correct combustion analyses or mass spectral data.
(5) Prepared in 37% yield by dripping (N_2) an 80/20 mixture of (*E*)- and (*Z*)-methyl 3-cyclopropyl-2-butenoate (Jorgensen, M.; Leung, T. *J. Am. Chem. Soc.* **1968**, *90*, 3769) through a heated (600 °C) quartz column packed with Pyrex beads.

(6) **2a**: ^1H NMR ($CDCl_3$, 270 MHz) δ 5.67 (1 H, t, J = 4.5 Hz, vinyl H), 5.47 (1 H, m, vinyl H), 3.78 (3 H, s, OCH_3), 3.58 (3 H, s, CO_2CH_3), 1.77 (3 H, m, vinyl CH_3); UV (EtOH) λ_{max} 271 nm (18 600); IR (neat) 1727 cm^{-1}; MS, m/e 312 (M^+). **2b**: IR (neat) 3400 (br d) cm^{-1}; UV (EtOH) λ_{max} 272 nm (10 500), MS, m/e 284 (M^+). **2c**: NMR ($CDCl_3$, 500 MHz) δ 6.49 (1 H, dd, J = 14.4, 6.8 Hz), 5.71 (1 H, t, J = 4.5 Hz), 5.38 (1 H, m), 4.15–3.85 (2 H, m), 3.77 (3 H, s, OCH_3), 1.64 (3 H, m, CH_3). **3a**: mp 116–117 °C (Et_2O); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.64 (1 H, dd, J = 3.7, 2.2 Hz, CHO), 5.20–4.80 (4 H, m, =CH_2), 3.79 (3 H, s, OCH_3), 1.14 (3 H, s, C_{18}-CH_3); IR (neat) 2735, 1720 cm^{-1}; UV (EtOH) λ_{max} 260 nm (18 200), 296 (sh, 3000); MS, m/e 310 (M^+). **3b**: ^1H NMR ($CDCl_3$, 270 MHz) δ 9.68 (1 H, d, J = 1.2 Hz, CHO), 3.85 (3 H, s, OCH_3), 1.05 (3 H, s, C_{18}-CH_3); IR (neat) 2735, 1740, 1720, 1670 cm^{-1}; MS, m/e 314 (M^+). **3c**: mp 106–108 °C (Et_2O); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.35 (1 H, s, CHO),[13] 3.84 (3 H, s, OCH_3), 2.81 and 2.74 (2 × 1 H, d, J = 18.2 Hz, CH_2CHO), 1.06 (3 H, s, C_{18}-CH_3); IR (neat film) 2735, 1740 (cyclopentanone), 1720 (CHO), 1670 (arom C=O) cm^{-1}; MS, m/e 314 (M^+). **4a**: ^1H NMR ($CDCl_3$, 270 MHz) δ 9.75 (1 H, t, J = 3.3 Hz, CHO), 5.20–4.80 (4 H, m, =CH_2), 3.79 (3 H, s, OCH_3), 1.40 (3 H, s, C_{18}-CH_3); UV (EtOH) λ_{max} 261 nm (14 000); IR (neat) 2730, 1720 cm^{-1}; MS, m/e 310 (M^+). **5a**: mp 89.5–90 °C (CH_2Cl_2–pentane); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.79 (1 H, t, J = 2.9 Hz, CHO), 5.00–4.70 (2 H, m, =CH_2), 3.80 (3 H, s, OCH_3), 2.00 (3 H, s, vinylic CH_3), 1.12 (3 H, s, C_{18}-CH_3); UV (EtOH) λ_{max} 276 nm (17 700). **5b**: ^1H NMR ($CDCl_3$, 90 MHz) δ 4.95–4.65 (2 H, m, =CH_2), 3.79 (3 H, s, OCH_3), 2.05 (3 H, s, OAc), 2.03 (3 H, s, vinylic CH_3), 1.01 (3 H, s, C_{18}-CH_3); MS, m/e 354 (M^+). **5c**: ^1H NMR ($CDCl_3$, 270 MHz) δ 9.74 (1 H, t, J = 2.9 Hz, CHO), 5.00–4.70 (2 H, m, =CH_2), 3.81 (3 H, s, OCH_3), 2.05 (3 H, s, vinylic CH_3), 1.29 (3 H, s, C_{18}-CH_3); UV (EtOH) λ_{max} 274 nm (12 000). **5d**: ^1H NMR ($CDCl_3$, 90 MHz) δ 4.95–4.65 (2 H, m, =CH_2), 3.80 (3 H, s, OCH_3), 2.05 (3 H, s, OAc), 2.00 (3 H, s, vinylic CH_3), 1.12 (3 H, s, C_{18}-CH_3); MS, m/e 354 (M^+). **6a**: mp 70.5–71.5 °C; IR (neat film) 1712 cm^{-1}; UV (EtOH) λ_{max} 274 nm (15 000); MS, m/e 312 (M^+); NMR ($CDCl_3$, 270 MHz) δ 3.80 (3 H, s, OCH_3), 3.75 (3 H, s, CO_2CH_3), 2.09 (3 H, m, C_{10}-CH_3), 1.98 (3 H, m). **7a**: mp 151–152 °C (CH_3OH, lit.[3a] mp 150–152 °C), ^1H NMR ($CDCl_3$, 270 MHz) δ 6.14 (1 H, m, C_{11}-H), 3.79 (3 H, s, OCH_3), 0.94 (3 H, s, C_{18}-CH_3); IR (CCl_4) 1740 cm^{-1}; UV (EtOH) λ_{max} 262 nm (17 300), 297 (sh, 3000); MS, m/e 282 (M^+). 8-iso-**7a**: mp 152–153.5 °C (lit.[3c] mp 149.5–150 °C, CH_3OH); ^1H NMR ($CDCl_3$, 90 MHz) δ 6.01 (1 H, m, C_{11}-H), 3.79 (3 H, s, OCH_3), 0.97 (3 H, s, C_{18}-CH_3); IR (CCl_4) 1735 cm^{-1}; UV (EtOH) λ_{max} 260 nm (17 000); MS, m/e 282 (M^+).[3c] **7b**: mp 142.5–144 °C, CH_3OH (lit.[3a] mp 142–144 °C).
(7) Adams, R. D.; Lim, H.; Ziegler, F. E. *Crystl. Struct. Commun.* **1982**, *11*, 575.

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