and Lp is the Lorentz–polarization correction.

The structural problem was solved and the model was refined as described previously.[1] Final refinement, treating the 37 carbons anisotropically and the 27 non-methyl hydrogens as fixed contributors,[19] produced an R value of 10.7% and an R_w of 10.5%. A final difference synthesis revealed the largest residual electron density was 0.41 e/Å^3, confirming the correctness of the structure.

Acknowledgment. N.F.W. acknowledges the financial support of the Petroleum Research Foundation, administered by the American Chemical Society, and the University of North Dakota Faculty Research Committee. The contributions of Donella Donmine, Robert Klun, Walter O. Carlson, and Dr. George Vesely toward the preparation and separation of **5** isomers are gratefully acknowledged. L.J.R. acknowledges the University of North Dakota for the contributions of computer time.

Registry No. (*Z,E,Z*)-**2**, 89726-81-8; **3**, 70456-59-6; (*E,E*)-**5**, 24815-65-4; (*E,Z*)-**5**, 89726-82-9; (*Z,Z*)-**5**, 80242-32-6; **6**, 89746-16-7; (*E*)-**7**, 55255-19-1; (*Z*)-**7**, 55255-18-0; deoxybenzoin hydrazone, 5171-96-0.

Supplementary Material Available: Tables of atomic coordinates (Table I), thermal parameters (Table II), bond distances (Table III), angles (Table IV), and intensity data (Table V) for photoproduct **2** (21 pages). Ordering information is given on any current masthead page.

(19) Theoretical positions for the 25 phenyl hydrogens and two olefin hydrogens were calculated at distances of 0.95 and 1.05 Å, respectively.

Ethyl 13,14-Dihydro-13,14-methyleneretinoates: Analogues of *all-trans*- and 13-*cis*-Retinoic Acid

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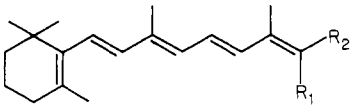
The synthesis of analogues of ethyl *all-trans*- and 13-*cis*-retinoates containing a 13,14-cyclopropyl moiety (**3** and **4**) as well as the identical analogues of ethyl 13-desmethyl-*all-trans*- and 13-*cis*-retinoates (**5** and **6**) is described. Wittig reaction between β-ionylideneethyltriphenylphosphonium bromide (**7**) and the appropriate formylcyclopropanecarboxylate afforded **3**/**4** and **5**/**6** in 79% yields as mixtures of their 11-*Z* and -*E* isomers. Purification of isomer mixtures by HPLC permitted stereochemical assignments after ^{1}H NMR analysis.

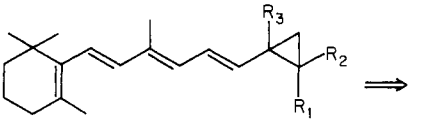
In 1967, 13-*cis*-retinoic acid (**1**) was identified in rat tissue extracts and was postulated to be a natural metabolite of *all-trans*-retinoic acid (**2**).[2] The isomer **1** has



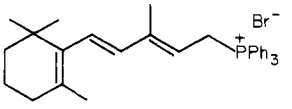
1, R_1 = COOH; R_2 = H
2, R_1 = H; R_2 = COOH

been found to be at least as effective as the parent compound **2** in promoting vitamin A dependent growth[3] as well as in controlling epithelial cell differentiation.[4] Recent work suggests that **1** is not solely produced as an artifact of isolation but that **2** is isomerized in mammals to some extent to **1**.[5] With a view toward studies of the significance of this reversible isomerization on biological activity, the rigid cyclopropyl analogues **3**–**6** have been prepared (Scheme I). The utility of **1** in treating dermatological conditions,[6] its tumor inhibitory properties,[7] and its reduced toxicity relative to the parent **2**[8] also supported the attractiveness of these cyclopropyl retinoids as synthetic candidates.

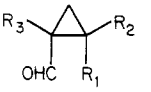
Scheme I



3, R_1 = CO_2Et; R_2 = H; R_3 = CH_3
4, R_1 = H; R_2 = CO_2Et; R_3 = CH_3
5, R_1 = CO_2Et; R_2 = H; R_3 = H
6, R_1 = H; R_2 = CO_2Et; R_3 = H



7

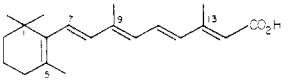


8, R_1 = CO_2Et; R_2 = H; R_3 = CH_3
9, R_1 = H; R_2 = CO_2Et; R_3 = CH_3
10, R_1 = CO_2Et; R_2 = H; R_3 = H
11, R_1 = H; R_2 = CO_2Et; R_3 = H

Retrosynthetic analysis (Scheme I) immediately suggested the classical "C_{15} + C_5" route to **3**–**6**.[9] This methodology had recently been successfully employed by Davalian and Heathcock for the preparation of the

(1) (a) National Cancer Institute Fellow, 1982–1984. (b) Program Project Grant No. AM-14881 of the National Institutes of Health.

(2) (a) Zile, M. H.; Emerick, R. J.; DeLuca, H. F. *Biochem. Biophys. Acta.* **1967**, *141*, 639–641. (b) To facilitate structural comparison, standard retinoic acid numbering has been used throughout:



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(4) Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413–3425.

(5) (a) Frolik, C. A.; Roller, P. P.; Roberts, A. B.; Sporn, M. B. *J. Biol. Chem.* **1980**, *255*, 8057–8062. (b) Zile, M. H.; Inhorn, R. C.; DeLuca, H. F. *Ibid.* **1982**, *257*, 3537–3543.

(6) Peck, G. L.; Olsen, T. G.; Yoder, F. W.; Strauss, J. S.; Downing, D. T.; Pandya, M.; Butkis, D.; Arnaud-Battandier, J. *New England J. Med.* **1979**, *300*, 329–333.

(7) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M. *Science (Washington, D.C.)* **1977**, *195*, 487–489.

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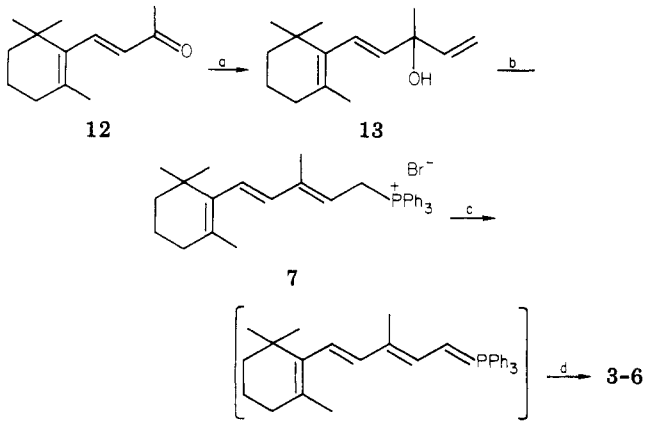
(9) Mayer, H.; Isler, O. In "Carotenoids"; Isler, O., Ed.; Birkhauser Verlag: Basel, 1971; Chapter 6.

0022-3263/84/1949-1941$01.50/0

Scheme II[a]



[a] (a) CH_2=CHMgBr, THF, 94%; (b) Ph_3P·HBr, MeOH, quantitative; (c) KO-*t*-Bu/benzene; (d) 8–11, benzene, 79%.

13,14-epoxide analogue of **2**.[10] Our syntheses concluded with the Wittig reaction between the known phosphonium salt **7**[11] and the appropriate formylcyclopropanecarboxylates **8–11**[12] as shown in Scheme II.

Phosphonium salt **7** was prepared by methods somewhat different than the classical route to this material.[13] Grignard reaction of vinylmagnesium bromide with β-ionone (**12**) in a manner similar to that of Ishikawa[14] afforded vinyl-β-ionol (**13**). Treatment of allylic alcohol **13** with Ph_3P·HBr in MeOH gave crude crystalline **7** quantitatively. This salt proved difficult to recrystallize without extensive decomposition and was generally used without further purification with no effect on its chemistry.

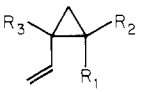
The cyclopropanes **8–11** were prepared as the appropriate cis/trans mixtures essentially according to the method of Payne.[12] Since useful quantities of all four retinoids **3–6** were desired, attempts were made to increase the amount of the thermodynamically less favored cis isomers (**8** and **10**) obtained in the cyclopropanation process.[15] Unfortunately, although these efforts were moderately successful (particularly for the mixture of **8** and **9**), the ratio of cis/trans formylcyclopropane was found to have little effect on product stereochemistry after Wittig reaction with the phosphorane derived from **7** (see below).

Among a number of base/solvent systems explored for the Wittig reaction between **7** and **8–11**, only KO-*t*-Bu/benzene was found to be satisfactory for the synthesis of **3–6**. Analysis of the resulting product mixtures by HPLC and ^{1}H NMR showed the presence of 30–50% of the *Z* isomers about the newly formed double bond corresponding to the $\Delta^{11,12}$ bond in **1** and **2**. These results are in contrast to those of Heathcock[10] where only trans olefination was reported when employing *n*-BuLi/Et_2O in the Wittig reaction. This method, however, was even less successful in the present case. Fortunately, exposure of a hexane solution of these (*Z*)-olefins to 0.01% by weight of I_2 quantitatively converted them to the all-*E* isomers **3–6**.

In addition, this Wittig reaction proved to be quite sluggish, especially with the neopentyl aldehydes **8**/**9**. As a result, equilibration at the carbethoxy moiety occurred to give about a 76:24 and 88:12 ratio of the trans/cis cyclopropyl retinoid isomers **4**/**3** and **6**/**5**, respectively, as a mixture of their 11-*Z*/*E* isomers. This product isomer ratio was obtained regardless of the ratio of the **8**/**9** and **10**/**11** employed in the reaction.

Assignments of product stereochemistry have been based principally on ^{1}H NMR analysis. In the ^{1}H NMR spectrum, the 12-^{1}H (retinoid numbering) in the 11-*Z* isomers clearly shows a cis coupling constant ($J_{11,12}$ = 10 Hz) while in the *E* isomers it shows the trans coupling constant of 14–16 Hz. Additionally, as mentioned above, the (*Z*)-olefins could be quantitatively isomerized to the presumably favored all-*E* isomers by I_2.

Product stereochemistry about the cyclopropane moiety was somewhat more difficult to assign for **3–6**. The demonstrated preference for the trans cyclopropanes in related studies[12,15,16] permitted tentative assignment of the trans configuration to the predominant isomers **4** and **6**. For **3** and **4**, the shift position of the quaternary methyl group further assisted in assignment of stereochemistry by comparisons with model compounds **14** and **15** (prepared as



14, R_1 = CO_2Et; R_2 = H; R_3 = CH_3
15, R_1 = H; R_2 = CO_2Et; R_3 = CH_3
16, R_1 = H; R_2 = CO_2Et; R_3 = H

a 3:7 mixture by Wittig reaction of a 3:7 mixture of **8**/**9** with methylidenetriphenylphosphorane). As might be expected, there is a measurable, but slight, downfield shift in the resonance of this methyl group (0.02–0.03 ppm) in the predominant isomers assigned as *trans*-**4** and -**15**. The absence of this methyl group has made stereochemical assignments more difficult for cyclopropanes **5** and **6**. Additionally, only the trans model compound **16** could be detected by ^{1}H NMR analysis when **10**/**11** was used in the Wittig reaction as above. This, coupled with the only slight differentiation of the methyl resonances in **3**/**4** and **14**/**15**, suggested that additional evidence was needed to make more certain assignments of product stereochemistry.

Paramagnetic lanthanide shift reagents have long been known to more strongly shift the signals of protons closer to functional groups in contact with the shift reagent.[17] This has permitted confirmation of the known stereochemistry in a number of molecules including cholesterol.[18] It was therefore anticipated that a relatively greater downfield shift in the resonance of the 12-^{1}H would occur in the cis isomers **3** and **5** as well as for the analogous proton in **14** when complexed with an appropriate mole ratio of tris(2,2,6,6-tetramethyl-3,5-heptane-4,6-dionato)-europium (Eu(thd)$_3$). As expected, when the ^{1}H NMR spectrum of the mixture of **14**/**15** in $CDCl_3$ was recorded in the presence of 0.5 molar equiv of Eu(thd)$_3$, the analogous vinyl proton assigned to **14** was shifted 0.08-ppm downfield while the corresponding proton in **15** was shifted by a negligible 0.01 ppm. Similarly, in the spectrum of **4** containing 0.5 molar equiv of Eu(thd)$_3$, the 12-^{1}H was shifted downfield only 0.01 ppm. Under identical conditions the 12-^{1}H in the spectrum of **3** was shifted 0.1 ppm. Virtually the same relationship was found for the desmethylcyclopropanes **5** and **6**. That is, with 0.5 molar equiv of shift reagent, the 12-^{1}H in **6** was only shifted 0.01 ppm

(10) Davalian, D.; Heathcock, C. H. *J. Org. Chem.* **1979**, 44, 4988–4990.
(11) Sarnecki, W.; Pommer, H. U.S. Patent 2950321, 1961; *Chem. Abstr.* **1961**, *55*, 4577.
(12) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351–3355.
(13) (a) Oroshnik, W.; Mebane, A. D. *J. Am. Chem. Soc.* **1949**, *71*, 2062–2065. (b) Pommer, H. *Angew. Chem.* **1960**, *72*, 811–819.
(14) Ishikawa, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 207–209.
(15) Curley, R. W., Jr.; DeLuca, H. F., *J. Org. Chem.*, following paper in this issue.
(16) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059–4068.
(17) Rabenstein, D. L. *Anal. Chem.* **1971**, *43*, 1599–1605.
(18) Hinckley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 5160–5162.

while the 12-^{1}H in **5** moved downfield 0.1 ppm, thereby confirming the assignment of cis stereochemistry to **3** and **5**.

Purification of sufficient quantities of **3–6** should permit a method of evaluation of the role of **1** in the biological activity of retinoic acid.

Experimental Section

All melting points, determined with a Thomas-Hoover capillary apparatus, and boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390, Nicolet NMC-200, or Bruker WH-270 spectrometer with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer 567 grating infrared spectrophotometer as liquid films. UV spectra were recorded with a Beckman Model 24 spectrophotometer. Electron-impact mass spectra and high-resolution mass spectra were obtained at 90 °C with an AEI MS-9 spectrometer equipped with a DS-50 data system. TLC was performed on silica gel 60 F_{254} precoated aluminum-backed plates from EM Reagents. Column chromatography was performed on silica gel 60, 70–230 mesh, from EM Reagents. Flash chromatography[19] was done on silica gel 60, 230–400 mesh, from EM Reagents. HPLC was carried out on a Beckman 332 gradient liquid chromatograph equipped with a Beckman 160 UV detector at a flow rate of 3.5 mL/min on the following columns: DuPont Zorbax-Sil (6.2 mm × 25 cm) and DuPont Zorbax-ODS (9.4 mm × 25 cm).

All manipulations of these light- and air-sensitive materials were performed under low-intensity gold fluorescent lighting. Commercial Ar was dried by bubbling through concentrated H_2SO_4. All organic solvents were appropriately dried prior to use.

Vinyl-β-ionol (13). In a round-bottomed flask equipped with Ar inlet, dropping funnel, magnetic stirrer, and $CaSO_4$ drying tube was dissolved 5.18 g (27 mmol) of β-ionone in 35 mL of dry THF. After cooling to 0 °C, 50 mL of 1 M vinylmagnesium bromide in THF (50 mmol) was added over 1 h. Stirring was continued at room temperature for 14 h. The solution was cooled to 0 °C, poured into 100 mL of ice-cooled saturated NH_4Cl, and then extracted 3 times with Et_2O. The combined organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl and then dried ($MgSO_4$). Concentration under reduced pressure afforded 5.90 g of **13** as a light yellow oil. Short-path vacuum distillation afforded 5.55 g (94%) of **13**: bp 110–111 °C (1.4 mmHg) [lit.[14] bp 113–115 °C (2 mmHg)]; TLC ($CHCl_3$/MeOH, 9:1) R_f 0.57; IR 3520, 2935, 1640, 920 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (s, 6, CH_3), 1.39 (s, 3, CH_3), 1.33–1.72 (m, 4, CH_2CH_2), 1.66 (s, 3, CH_3), 1.80–2.09 (m, 2, $CH_2(CH_3)C$=), 4.99–6.19 (m, 5, vinyl).

β-Ionylideneethyltriphenylphosphonium Bromide (7). In a round-bottomed flask equipped with an Ar inlet, dropping funnel, magnetic stirrer, and $CaSO_4$ drying tube was suspended 4.0 g (11 mmol) of Ph_3P·HBr[20] in 40 mL of dry MeOH. A solution of 2.5 g (11 mmol) of **13** in 40 mL of dry MeOH was added dropwise over 30 min. Stirring was continued at room temperature for 75 h and then the solution was concentrated under reduced pressure. After a further 2.5 h at 0.5 mmHg, **7** was obtained as a glass. Crystallization from Et_2O/THF (40:1) afforded 5.96 g (100%) of **7**. Recrystallization of a portion from acetone/hexanes (1:1) returned 64% of **7** as faint yellow cubes: mp 135–137 °C (lit.[11] mp 135–137 °C); NMR (Me_2SO-d_6) δ 0.94 (s, 6, CH_3), 1.39 (s, 3, CH_3), 1.29–1.64 (m, 4, CH_2CH_2), 1.58 (s, 3, CH_3), 1.93 (m, 2, $CH_2(CH_3)C$=), 4.64 (dd, 2, CH_2P, $J_{H,H}$ = 6 Hz, $J_{H,P}$ = 15 Hz), 5.42 (m, 1, $CHCH_2$), 6.01 (s, 2, CH=CH), 7.75 (m, 15, C_6H_5).

Ethyl *cis*- and *trans*-13,14-Dihydro-13,14-methyleneretinoates (3 and 4). To an oven-dried, round-bottomed flask equipped with a magnetic stirrer, Ar inlet, dropping funnel, and $CaSO_4$ drying tube was added a suspension of 540 mg (1 mmol) of **7** in 5 mL of dry benzene. To this was added 115 mg (1 mmol) of KO-*t*-Bu. The resulting deep red solution was stirred for 15 min, and then a solution of 156 mg (1 mmol) of **8**/**9**[12,15] in 5 mL of dry benzene was added dropwise over 10 min. The solution was stirred for 22 h at room temperature during which time the solution gradually became very light red. After addition of 10 mL of Et_2O and cooling in an ice-bath, 10 mL of 0.1 N HCl was added and the organic layer was removed after extraction. The aqueous layer was washed with two additional 10-mL portions of Et_2O, and the combined organic extracts were washed with water, then saturated NaCl, and then dried (Na_2SO_4). Drying agent was removed by vacuum filtration, and the solution was concentrated under reduced pressure to afford a light red semisolid. Early fractions from rapid column chromatography ($CHCl_3$ elution) were combined and concentrated under reduced pressure to a light yellow oil. Flash chromatography of this oil with 8% Et_2O/petroleum ether afforded 270 mg (79%) of retinoid isomers after concentration under reduced pressure. This oil showed TLC R_f 0.3 (8% Et_2O/petroleum ether). HPLC analysis (Zorbax-Sil; 0.1% Et_2O/hexane) showed the presence of four isomers eluting with the following retention times and relative percentages: t_R 12 min (37%); t_R 13 min (18%); t_R 14.5 min (7%); t_R 15.5 min (38%). ^{1}H NMR analysis showed the two rapidly eluting isomers to be the 11-*Z* isomers while purification of the third and fourth components allowed their identification as 11-*E* isomers **3** and **4**, respectively. **3**: IR 2958, 1724 cm^{-1}; UV (hexane) λ_{max} 296 nm (ε 26 660); NMR ($CDCl_3$) δ 1.03 (s, 6, $(CH_3)_2C$), 1.26 (t, 3, $CO_2CH_2CH_3$, J = 7 Hz), 1.36 (s, 3, 13-CH_3), 1.74 (s, 3, 5-CH_3), 1.92 (s, 3, 9-CH_3), 4.14 (q, 2, CO_2CH_2, J = 7 Hz), 5.28 (d, 1, 12-H, J = 14 Hz), 5.88–6.68 (m, 3, vinyls); MS, m/e (relative intensity) $(M)^+$ 342 (100), 327 (11), 297 (10); HRMS, m/e required for $C_{23}H_{34}O_2$ 342.2559, observed 342.2561. **4**: IR 2960, 1738 cm^{-1}; UV (hexane) λ_{max} 298 nm (ε 27 070); NMR ($CDCl_3$) δ 1.01 (s, 6, $(CH_3)_2C$), 1.27 (t, 3, $CO_2CH_2CH_3$, J = 7 Hz), 1.38 (s, 3, 13-CH_3), 1.70 (s, 3, 5-CH_3), 1.92 (s, 3, 9-CH_3), 4.13 (q, 2, CO_2CH_2, J = 7 Hz), 5.35 (d, 1, 12-H, J = 14 Hz), 5.88–6.68 (m, 3, vinyls); MS, m/e (relative intensity) $(M)^+$ 342 (100), 327 (11), 297 (10); HRMS, m/e required for $C_{23}H_{34}O_2$ 342.2559, observed 342.2550.

Addition of 0.5 molar equiv of $Eu(thd)_3$ to the $CDCl_3$ solution of **3** shifted the ^{1}H NMR resonance of the 12-^{1}H downfield to 5.38 ppm while the position of the 12-^{1}H in **4** was only moved to 5.36 ppm.

Ethyl *cis*- and *trans*-13,14-Dihydro-13-desmethyl-13,14-methyleneretinoates (5 and 6). Wittig reaction as above between 71 mg (0.5 mmol) of **10**/**11**[12,15] and the ylide prepared from 272 mg (0.5 mmol) of **7** and 56 mg (0.5 mmol) of KO-*t*-Bu appeared complete within 8 h. Workup and chromatography as for **3**/**4** afforded 130 mg (79%) of retinoid isomers after flash chromatography. This oil showed TLC R_f 0.2 (6% Et_2O/petroleum Et_2O). HPLC analysis (Zorbax-Sil; 0.1 % Et_2O/hexane) showed the presence of four isomers eluting with the following retention times and relative percentages: t_R 11.5 min (26%), t_R 12.5 min (7%); t_R 13.5 min (5%); t_R 14.5 min (62%). The second and third eluting isomers were further purified by reverse-phase HPLC (Zorbax-ODS; 7.5% H_2O/MeOH). ^{1}H NMR analysis as well as I_2 isomerization showed the first and third isomers to be the 11-*Z* isomers while the second and fourth components were identified as the 11-*E* isomers **5** and **6**, respectively. **5**: IR 2935, 1728 cm^{-1}; UV (hexane) λ_{max} 296 nm (ε 26 400); NMR ($CDCl_3$) δ 0.97 (s, 6, $(CH_3)_2C$), 1.20 (t, 3, $CO_2CH_2CH_3$, J = 8 Hz), 1.67 (s, 3, 5-CH_3), 1.86 (s, 3, 9-CH_3), 4.06 (q, 2, CO_2CH_2, J = 8 Hz), 5.11 (dd, 1, 12-H, $J_{11,12}$ = 16 Hz, $J_{12,13}$ = 8 Hz), 5.76–6.66 (m, 3, vinyls); MS, m/e (relative intensity) $(M)^+$ 328 (100), 313 (18), 283 (13); HRMS, m/e required for $C_{22}H_{32}O_2$ 328.2402, observed 328.2400. **6**: IR 2935, 1724 cm^{-1}; UV (hexane) λ_{max} 299 nm (ε 29 590); NMR ($CDCl_3$) δ 1.02 (s, 6, $(CH_3)_2C$), 1.28 (t, 3, $CO_2CH_2CH_3$, J = 8 Hz), 1.70 (s, 3, 5-CH_3), 1.91 (s, 3, 9-CH_3), 4.14 (q, 2, CO_2CH_2, J = 8 Hz), 5.26 (dd, 1, 12-H, $J_{11,12}$ = 16 Hz, $J_{12,13}$ = 8 Hz), 5.92–6.66 (m, 3, vinyls); MS, m/e (relative intensity) $(M)^+$ 328 (100), 313 (20), 283 (13); HRMS, m/e required for $C_{22}H_{32}O_2$ 328.2402, observed 328.2394.

Addition of 0.5 molar equiv of $Eu(thd)_3$ to the $CDCl_3$ solution of **5** shifted the ^{1}H NMR resonance of the 12-^{1}H downfield to 5.21 ppm while the position of the 12-^{1}H in **6** was virtually unchanged at 5.27 ppm.

Ethyl *cis*- and *trans*-2-Vinyl-2-methylcyclopropanecarboxylate (14 and 15). Wittig reaction of 312 mg (2 mmol) of **8**/**9**[12] with methylidenetriphenylphosphorane (prepared from 714 mg (2 mmol) of methyltriphenylphosphonium bromide and 224 mg (2 mmol) of KO-*t*-Bu as above provided a crude oil. Column chromatography with $CHCl_3$/MeOH (99:1) elution afforded 299 mg (97%) of **14**/**15**: TLC ($CHCl_3$/MeOH, 10:1) R_f

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

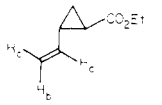
(20) Schwieter, U.; Planta, C. v.; Ruegg, R.; Isler, O. *Helv. Chim. Acta* **1962**, *45*, 541–548.

0.72; UV (hexane) λ_{max} 203 nm (ϵ 4450); IR 2990, 1728, 1640, 905 cm^{-1}.

^1H NMR analysis suggested the presence of 14/15 in a ratio of 3:7. Selective decoupling experiments permitted assignments of certain resonances to the appropriate isomer: NMR ($CDCl_3$) δ 1.11 (m, 1), 1.27 (dt, 3, $COCH_2CH_3$), 1.31 (s, cis CH_3), 1.34 (s, trans CH_3), 1.43 (m, 1), 4.15 (dq, 3, $COCH_2CH_3$), 4.97-5.21 (m, 2, CH_2=CH), 5.46 (dd, 1, trans CH_2=CH, J_{trans} = 16 Hz, J_{cis} = 10 Hz), 5.96 (dd, 1, cis CH_2=CH, J_{trans} = 16 Hz, J_{cis} = 10 Hz).

Addition of 0.5 molar equiv of $Eu(thd)_3$ to the $CDCl_3$ solution of 14/15 shifted the ^1H NMR resonances of the *trans*-CH_2=CH to 5.47 ppm while the *cis*-CH_2=CH was moved to 6.04 ppm.

Ethyl *trans*-2-Vinylcyclopropanecarboxylate (16). Wittig reaction of 284 mg (2 mmol) of 10/11 with methylidenetriphenylphosphorane prepared as above provided a crude oil. Column chromatography with $CHCl_3$/MeOH (99:1) elution afforded 225 mg (80%) of 16: TLC ($CHCl_3$/MeOH, 10:1) R_f 0.71; UV (hexane) λ_{max} 207 nm (ϵ 4960); IR 2990, 1729, 1640, 910 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (m, 1), 1.26 (t, 3, $CO_2CH_2CH_3$), 1.38 (m, 1), 1.64 (m, 1), 2.01 (m, 1), 4.14 (q, 2, $CO_2CH_2CH_3$), 4.99 (d, 1, H_b, J = 10 Hz), 5.16 (d, 1, H_c, J = 16 Hz), 5.44 (dd, 1, H_a, J_{trans} = 16 Hz, J_{cis} = 10 Hz).



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Registry No. (11*E*)-3, 89827-98-5; (11*Z*)-3, 89887-36-5; (11*E*)-4, 89887-37-6; (11*Z*)-4, 89887-38-7; (11*E*)-5, 89827-99-6; (11*Z*)-5, 89887-39-8; (11*E*)-6, 89887-40-1; (11*Z*)-6, 89887-41-2; 7, 62285-98-7; 8, 13950-14-6; 9, 13949-97-8; 10, 13950-12-4; 11, 13949-93-4; 12, 79-77-6; 13, 31821-03-1; 14, 52345-63-8; 15, 52345-60-5; 16, 2183-90-6; CH_2=CHBr, 593-60-2.

A Study of the Stereoselectivity of Cyclopropanation of Some α,β-Unsaturated Aldehydes by Ethyl (Dimethylsulfuranylidene)acetate

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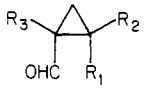
The effect of aprotic solvent polarity on the stereoselectivity of cyclopropanation of the α,β-unsaturated aldehydes methacrolein and acrolein by ethyl (dimethylsulfuranylidene)acetate has been investigated. The proportion of less favored cis cyclopropane isomer was found to increase linearly with the log of the solvent dielectric constant. This effect of solvent on stereoselectivity was much more pronounced with the more sterically demanding substrate methacrolein. Stability and kinetic studies suggest that this effect is due to an increased reaction rate in the more polar solvents. A general mechanism for the reaction is proposed that seems to account for the experimental observations.

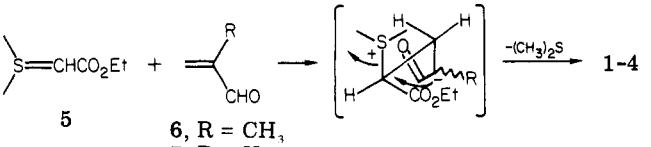
During the course of synthesis of some analogues of *all-trans*- and 13-*cis*-retinoic acid,[2] we required useful quantities of the four 2-formylcyclopropanecarboxylates 1-4. These formyl esters were prepared by Payne[3] by the



1, R_1 = CO_2Et; R_2 = H; R_3 = CH_3
2, R_1 = H; R_2 = CO_2Et; R_3 = CH_3
3, R_1 = CO_2Et; R_2 = H; R_3 = H
4, R_1 = H; R_2 = CO_2Et; R_3 = H

reaction of the stabilized sulfur ylide 5 with the appropriate α,β-unsaturated aldehydes, presumably through a dipolar intermediate as shown in Scheme I.[4,5] With both methacrolein (6) and acrolein (7) as substrate, predominantly trans cyclopropanation to give 2 and 4, respectively (GLC analysis), was observed under the reported conditions.[3] Since we desired essentially equal quantities of 1-4, an examination of the effect of solvent polarity on product cis/trans isomer ratios seemed warranted for this cyclopropanation. This was of especial interest since aprotic solvent polarity markedly influences reaction stereose-

Scheme I



5 6, R = CH_3 7, R = H

Table I. Effect of Solvent Polarity on Cyclopropane Stereochemistry[a]

substrate	solvent	dielectric constant,[b] 20 °C	products,[c] rel % cis	products,[c] rel % trans	lit. cis/trans[d]
6	C_6H_6	2.28	30 (9.37)	70 (8.87)	32:68
6	THF	7.58	35	65	
6	CH_2Cl_2	9.08	41	59	
6	Me_2CO	20.70	45	55	
6	CH_3CN	37.50	48	52	
7	C_6H_6	2.28	8.5 (9.35)	91.5 (9.31)	
7	Me_2CO	20.70	14.5	85.5	17:83

[a] All reactions were run for 18 h at 25 °C under an Ar atmosphere. [b] Schneider, R. L. *Eastman Org. Chem. Bull.* **1975**, *47*, 1-12. [c] Determined by HPLC analysis and integration of the ^1H NMR spectrum after purification. δ values in parentheses are the chemical shifts of the aldehydic protons ($CDCl_3$). [d] See ref 3.

(1) (a) National Cancer Institute Fellow, 1982-1984. (b) Program Project Grant No. AM-14881 from the National Institutes of Health.
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