technical assistance, Dr. E. B. Whipple for NOE NMR experiments, and Dr. J. F. Blake for computational analysis.

Registry No. 1, 138126-72-4; 2, 126642-39-5; 7 (isomer 1), 138785-49-6; 7 (isomer 2), 138875-10-2; 8, 138785-50-9; 8 (reduced alcohol, isomer 1), 138785-56-5; 8 (reduced alcohol, isomer 2), 138875-09-9; 9, 138006-41-4; 10, 138785-51-0; 11 (isomer 1), 138785-52-1; 11 (isomer 2), 138785-54-3; 12 (isomer 1), 138785-53-2; 12 (isomer 2), 138785-55-4; 13 (isomer 1), 138875-07-7; 13 (isomer 2), 138875-08-8; 3-bromo-5-chloropyridin-2-one, 137628-16-1; 2-amino-3-bromo-5-chloropyridine, 26163-03-1.

Supplementary Material Available: NMR data for compounds 9, 11, 12, 13, and 3-bromo-5-chloropyridin-2-one (6 pages). Ordering information given on any current masthead page.

Selectivity in [2 + 3] and [4 + 3] Annulations. Cope Rearrangement of (Silyloxy)divinylcyclopropane Systems Leading to Functionalized Bicyclo[3.2.*n*]alkenyl Derivatives

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Recently, we reported a mild, low-temperature procedure for the vinylcyclopropane–cyclopentene rearrangement (i.e. 2 → 4, Figure 1) that occurs at −78 °C in those systems where the vinyl moiety is terminated with a silyl enol ether.[1] With the availability of such mild conditions, the utility of the [2 + 3] cyclopentene annulation, previously possible only through thermolytic rearrangements,[2-5] can now be expressed in the synthesis of systems containing sensitive functionalities. The cyclopropanation of enones using ester dienolate anions rather than carbenoid species has been reported in 1986 for the nor-silyloxy derivatives of 1[4] and extended to the (silyloxy)bromocrotonate 1 in 1990.[1] A report was also published on the potential selectivity between the cyclopentene mode of the rearrangement (2 → 4) and the divinylcyclopropane–cycloheptadiene (Cope) rearrangement (2 → 3).[3] In this paper we report on the selectivity of silyl enol ether-terminated vinylcyclopropanes of type 2 to undergo either a cyclopentene rearrangement or, upon conversion to their enol ethers or enolate anions, the divinylcyclopropane–cycloheptadiene rearrangement.

The lithium dienolate of 1 was generated at −100 °C as previously reported[1] and allowed to add to cyclopentenone or cyclohexenone, providing cyclopropanes **5a,b** and **6a,b**, respectively. The stereochemistry of enol ethers was shown to be *E* in all cases (as evidenced by the value of coupling constants, J = 11.9–12.1 Hz). The cyclopropanes were obtained as mixtures of exo and endo isomers (denoting the position of vinyl group) in the ratio of 57/43 for **5** and 50/50 for **6**.

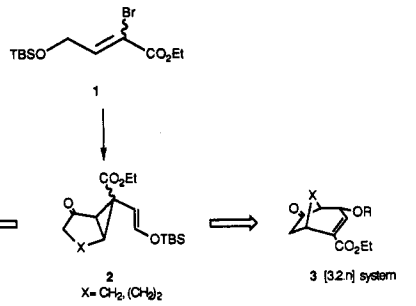
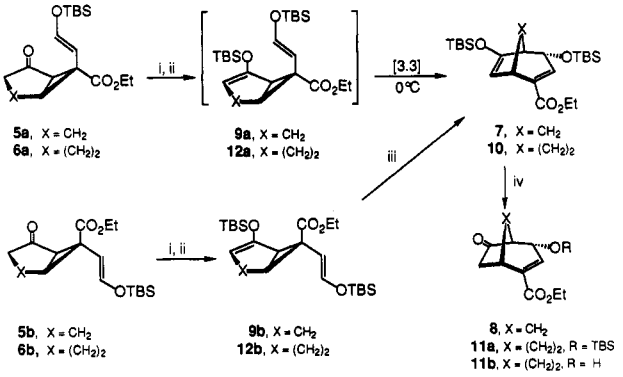
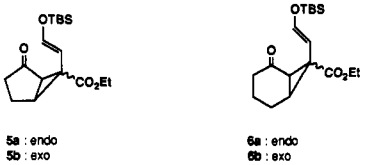


Figure 1. Cyclopentene vs cycloheptadiene (Cope) rearrangement.

Scheme I[a]



[a] (i) LDA, THF, −78 °C; (ii) TBSCl, HMPA, −78 °C → 0 °C (or rt); (iii) 150 °C, C_6H_6, sealed tube; (iv) 1 M HCl, THF, rt.



From other studies it is now known that the lithium dienolate anions derived from esters of α-bromocrotonates are mixtures of *E*/*Z* species (with respect to the enolate anion double bond).[6] This indicates a nonstereospecific addition to the enone, in contrast to the well-known stereospecificity observed for the Michael addition of ester enolates to enones.[7]

Treatment of the endo isomer **5a**[2,8] with LDA at −78 °C resulted in the formation of the lithium enolate anion, which underwent the Cope rearrangement[9,10] at room temperature to give a chromatographically inseparable

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(8) The yields of **5** and **6** could be improved significantly by careful control of the temperature and the addition rate of the enone solution in THF to the solution of lithium dienolate derived from **1**.
(9) For reviews of the Cope rearrangement, see: (a) Mil'vitskaya, E. M.; Tarakanova, A. V.; Plate, A. F. *Russ. Chem. Rev.* **1976**, *45*, 469. (b) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (c) Piers, E. In *Comprehensive Organic Chemistry*; Pergamon: Oxford, 1991, in press. (d) Hudlicky, T.; Rulin, F.; Reed, J. W.; Gadamasetti, R. G. *Org. React.* **1992**, *41*, 1. For reviews on vinylcyclopropane–cyclopentene rearrangement, see: (e) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1989**, *33*, 247. (f) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 899.
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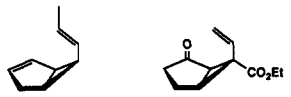
mixture of 8 and starting material **5a** (8/**5a** = 2:1),[11] Scheme I. When the temperature of the reaction mixture was raised to 50 °C, the formation of the Cope product increased about 2-fold (8/**5a** = 4:1).[11] Interestingly, when the enolate anion was trapped with TBSCl at −78 °C and then the mixture was warmed up slowly, the primary Cope product **7** was formed at 0 °C as the sole product. Hydrolysis of **7** with dilute aqueous HCl solution in THF in 1 h afforded 8 (74% from **5a**).

The intermediate silyl enol ether **9b** isolated from the reaction of the exo isomer **5b** with LDA followed by TBSCl at −78 °C was thermally stable at room temperature and was subjected to the thermolysis[10] in dry benzene in a sealed tube at 150 °C for 8 h to give **7** in 95% yield.

Similar results were observed with the isomers **6a,b** of vinylcyclopropane ketones derived from cyclohexenone. The lithium enolate anion formed from the reaction of the endo isomer **6a** with LDA at −78 °C rearranged to **11a** at room temperature. The corresponding silyl enol ether of **6a** (LDA/TBSCl, −78 °C) yielded the Cope product **10** at 0 °C. Prolonged acid hydrolysis of **10** (4 h) resulted in the removal of two silyl groups to produce alcohol **11b** (78% from **6a**). The intermediate silyl enol ether **12b** of the exo isomer **6b** rearranged to **10** at 150 °C (dry benzene, sealed tube) in 88% yield.

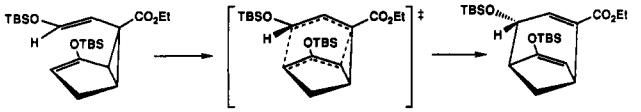
The observation that 6-*endo*-vinylbicyclo[3.1.0]hex-2-ene (**13**)[12] had a half-life of 1 day at 25 °C and that the *potassium* enolate anion of the endo isomer of 6-carbethoxy-6-vinylbicyclo[3.1.0]hexan-2-one (**14**) rearranged at room temperature[2] led to the suggestion of a remote charge acceleration in the divinylcyclopropane Cope rearrangement.[2,13] However the *lithium* enolate anion of **14** did not



13 14

undergo the rearrangement,[2] in contrast to the lithium salt of **5a** and **6a**, which gave the corresponding products at room temperature. Therefore, the presence of the silyloxy group situated at one of the reaction centers (vinylic position) must somehow account for the facile Cope rearrangement of the lithium enolate anions of **5a** and **6a** as well as of the corresponding silyl enol ethers. Moreover, the remote charge acceleration in the Cope rearrangement of the alkoxide of divinylcyclopropane systems could depend upon the position of the alkoxide group. We are aware of at least one example of enolate anion accelerated Cope rearrangements.[14]

It has been suggested that the [3.3] sigmatropic rearrangement of *cis*-divinylcyclopropane systems would proceed via a boatlike transition state.[9] Consequently, the hydrogen at C-4 in 8 and/or 11 would have an exo configuration. The stereochemical assignment at C-4 was confirmed by ^{1}H NMR experiments. Suitable decoupling experiments revealed that the coupling constants $J_{4,5}$ (5.9 Hz) and $J_{4,3}$ (2.6 Hz) of H-4 would be expected to be smaller and larger, respectively, due to the corresponding dihedral angles (molecular models) if this proton possesses the endo configuration. Furthermore, in an NOE experiment, the irradiation of the H-4 caused an enhancement at H-8b.



9a 15 7

The thermal transformation of exo isomers **9b** and **12b** on the other hand are likely to proceed via a one-center epimerization, which occurs via diradical intermediates[15] to afford the corresponding endo isomers. The presence of the carbethoxy group could assist in stabilizing the diradical intermediates.[10b] These isomers were readily converted to **7** and **10**.

The four vinylcyclopropanes discussed here also undergo a facile low-temperature vinylcyclopropane–cyclopentene rearrangement with TMSI/HMDS at −50 °C or *n*-Bu_4NF/THF at −20 °C, as previously reported.[1] The precise mechanism of these rearrangements is not known at this time.

In conclusion, it proved possible to mediate the mode of rearrangement of vinylcyclopropanes **2** to *either* fused *or* bridged bicyclic manifolds by judicious choice of conditions. Although the mechanistic details of either rearrangement can only be speculated upon at this time,[16] the achieved practical selectivity will find use in the synthesis of oxygenated systems of this type. Studies on the mechanism and extension of this technology to include asymmetric induction are in progress and will be reported in due course.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were obtained in $CDCl_3$ at 200 or 270 MHz. Multiplicities designated ca, were complex absorptions.

Analytical TLC was performed on precoated silica gel 60 F_{254} plates from Merck and visualization was accomplished with 254-nm UV light and/or an acidic solution of anisaldehyde in methanol with heating. Flash column chromatography was performed according to Still[17] on EM Science silica gel 60 (230–400 mesh).

Reactions which required anhydrous conditions were performed in glassware that had been flame-dried and cooled under Ar. THF and diethyl ether were dried over sodium benzophenone and distilled prior to use; hexane and benzene were distilled over CaH_2 and stored over 4A molecular sieves. Starting materials vinylcyclopropane ketones **5** and **6** were prepared according to the known procedure.[2]

General Procedure for Silylation of Vinylcyclopropane Ketones 5 and 6. To a stirred solution of LDA (1.2 equiv, 0.36 mmol) in THF (3 mL) at −78 °C was added dropwise a solution of the ketone (0.3 mmol) in THF (1 mL), and the mixture was stirred for 45 min. After addition of a solution of TBSCl (1.5

(11) Product ratios were estimated by ^{1}H NMR analysis.
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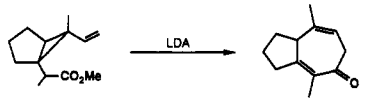
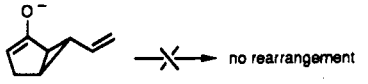


(b) Piers, E. Unpublished observations:



(15) Baldwin, J. E.; Gilbert, K. E. *J. Am. Chem. Soc.* **1976**, *98*, 8283.
(16) One of the referees commented on the distinction of diradical vs concerted mechanism in the divinylcyclopropane–cycloheptadiene isomerization. Our mechanistic rationale is based on the generally accepted thought that the cis systems rearrange with a low E_{act} and are thought to proceed in a concerted manner while the trans isomers require a diradical isomerization to the cis compounds via a higher E_{act} at (usually) higher temperatures. Under such conditions any cis isomer formed is immediately transformed to products.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

equiv, 0.45 mmol) and HMPA (2 equiv, 0.6 mmol) in THF (1 mL), the reaction mixture was stirred at −78 °C for 45 min and then at rt for 3 h, followed by quenching with cold saturated $NaHCO_3$ solution. The aqueous phase was extracted with hexane. The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave crude silyl enol ether.

Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-6-oxobicyclo-[3.2.1]oct-2-ene-2-carboxylate (8). Following the general procedure for silylation of **5a** [(90 mg, 0.28 mmol); LDA (0.34 mmol); TBSCl (62 mg, 0.41 mmol); HMPA (0.56 mmol)], 107 mg (88%) of the crude silyl enol ether **7** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.28–6.30 (ca, 1 H), 5.19 (d, 1 H, J = 3.0 Hz), 4.49 (dd, 1 H, J = 5.2, 2.8 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 3.07–3.10 (ca, 1 H), 2.67 (br ddd, 1 H, J = 5.2, 5.0, 1.4 Hz), 2.23 (ddd, 1 H, J = 10.0, 5.2, 5.0 Hz), 1.70 (d, 1 H, J = 10.0 Hz), 1.29 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 6 H), 0.12 (s, 3 H).

To a stirred solution of **7** in THF (3 mL) was added 2 mL of 1 M HCl solution. After being stirred at rt for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvent gave a crude product which was purified by flash column chromatography (silica gel, gradient elution, 5–20% EtOAc in hexane) to afford **8** (67 mg, 74%): R_f = 0.40 (hexane/EtOAc, 4:1); IR (film) ν_{max} 2956, 2931, 1746, 1716, 1642, 1258, 1107, 1063, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (dd, 1 H, J = 2.6, 1.2 Hz), 4.65 (dd, 1 H, J = 5.9, 2.6 Hz), 4.23 (q, 2 H, J = 7.2 Hz), 3.31–3.37 (ca, 1 H), 2.61 (br dd, 1 H, J = 5.9, 5.6 Hz), 2.37–2.45 (ddd, 1 H, J = 18.0, 6.0, 1.0 Hz), 2.23–2.32 (dd, 1 H, J = 18.0, 3.2 Hz), 2.08–2.15 (ddd, 1 H, J = 12.0, 5.6, 4.2 Hz), 1.96–2.03 (br dd, 1 H, J = 12.0, 3.2 Hz), 1.31 (t, 3 H, J = 7.2 Hz), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.3, 165.8, 138.4, 137.9, 70.7, 60.9, 52.1, 48.8, 35.1, 32.1, 25.7, 18.2, 14.2, −4.7, −4.8; MS (EI, 70 eV) m/z (rel intensity) 324 (11, M^+), 309 (100), 193 (50), 75 (57); exact mass calcd for $C_{17}H_{28}O_4Si$ 324.1756, found 324.1748.

Ethyl 4-Hydroxy-6-oxobicyclo[3.2.2]non-2-ene-2-carboxylate (11b). Following the general procedure for silylation of **6a** [(100 mg, 0.30 mmol); LDA (0.36 mmol); TBSCl (70 mg, 0.45 mmol) and HMPA (0.6 mmol)], 115 mg (86%) of the silyl enol ether **10** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.45–6.48 (ca, 1 H), 5.34 (dd, 1 H, J = 8.1, 2.2 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 4.11 (dd, 1 H, J = 4.4, 4.2 Hz), 3.48–3.53 (ca, 1 H), 2.60–2.64 (ca, 1 H), 1.86–1.98 (m, 1 H), 1.47–1.69 (m, 3 H), 1.29 (t, 3 H, J = 7.1 Hz), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.12 (s, 12 H); exact mass calcd for $C_{24}H_{45}O_4Si_2$ 453.2856, found 453.2863.

A mixture of the silyl enol ether **10**, 1 M HCl solution (2 mL), and THF (4 mL) was stirred at rt for 4 h. The cooled reaction mixture was diluted with CH_2Cl_2 and poured into a saturated $NaHCO_3$ solution. The aqueous phase was extracted thoroughly with CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave a crude product, which was purified by flash column chromatography (silica gel, 10% deactivated with H_2O; hexane/EtOAc, 1:1) to yield **11b** (52 mg, 78%), as a white solid from ether: mp 91.5 °C (ether); R_f = 0.35 (hexane/EtOAc, 2:3); IR (KBr) ν_{max} 3388, 3002, 2948, 1716, 1690, 1654, 1255, 1185, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86–6.88 (ca, 1 H), 4.50 (dd, 1 H, J = 4.0, 3.9 Hz), 4.22 (q, 2 H, J = 7.1 Hz), 3.52 (ca, 1 H), 2.82–2.86 (br dd, 1 H, J = 5.8, 4.4 Hz), 2.54 (d, 2 H, J = 3.7 Hz), 1.82–2.18 (m, 4 H), 1.31 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 212.3, 153.2, 139.7, 139.3, 72.9, 61.3, 53.5, 47.2, 28.9, 25.3, 19.9, 14.1; MS (EI, 70 eV) m/z (rel intensity) 224 (M^+, 30), 195 (51), 178 (81), 136 (34), 107 (34), 91 (58), 79 (65), 55 (100). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.19.

Thermolysis of 9b. Following the general procedure for silylation of **5b** [(198 mg, 0.6 mmol); LDA (0.72 mmol); TBSCl (135 mg, 0.9 mmol); HMPA (0.6 mmol)], 230 mg (86%) of **9b** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.41 (d, 1 H, J = 12.1 Hz), 5.06 (d, 1 H, J = 12.1 Hz), 4.23 (br s, 1 H), 3.99–4.14 (m, 2 H), 2.48–2.54 (m, 2 H), 1.93–1.96 (m, 1 H), 1.75–1.80 (m, 1 H), 1.21 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.12 (s, 6 H).

A solution of **9b** (138 mg, 0.3 mmol) in dry benzene (5 mL) was placed in a pyrolysis tube and degassed. The tube was cooled with liquid nitrogen, sealed under vacuum, and then heated in a sand bath (150 °C) for 8 h. The tube was cooled to rt and unsealed. Removal of the solvent gave 132 mg (95%) of **7**.

Thermolysis of 12b. Following the general procedure for silylation of **6b** [(208 mg, 0.61 mmol); LDA (0.73 mmol); TBSCl (137 mg, 0.9 mmol); HMPA (1.2 mmol)], 241 mg (86%) of **12b** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.42 (d, 1 H, J = 12.0 Hz), 5.16 (d, 1 H, J = 12.0 Hz), 4.67 (dd, 1 H, J = 5.4, 2.7 Hz), 4.09 (q, 2 H, J = 7.1 Hz), 1.95–2.10 (m, 2 H), 1.67–1.79 (m, 2 H), 1.52–1.58 (m, 1 H), 1.45 (d, 1 H, J = 8.8 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.19 (s, 3 H), 0.16 (s, 3 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 147.4, 143.8, 112.8, 101.0, 60.5, 34.9, 27.1, 26.3, 25.7, 21.2, 18.0, 16.9, 14.0, −4.4.

Silyl ether **12b** (97 mg) was subjected to the thermolysis following the same procedure as described above to give 86 mg (88%) of **10**.

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Registry No. 5a, 127179-60-6; **5b**, 127179-59-3; **6a**, 127085-76-1; **6b**, 127179-61-7; **7**, 138878-69-0; **8**, 138878-70-3; **9b**, 138878-71-4; **10**, 138878-72-5; **11b**, 138878-68-9; **12b**, 138878-67-8.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **7**, **8**, **9b**, **10**, **11b**, and **12b** (9 pages). Ordering information is given on any current masthead page.

An Improved Procedure for the Introduction of the δ-Lactone Portion of HMG-CoA Reductase Inhibitors

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In 1985, Heathcock published the synthesis of the ketophosphonate **1** and demonstrated its use in the preparation of the hypocholesterolaemic HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor compactin.[1] Subsequently, **1** has been used in the synthesis of other mevinic acids including dihydromevinolin,[2] as well as monocyclic[3] and heterocyclic[4] analogues of these compounds.

The coupling of **1** with aldehydes represents an attractive approach to the synthesis of this clinically important series of compounds since it introduces the crucial dihydroxy acid side chain as a single unit that can be easily

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