222.1090. LRMS (EI) m/e: 222 (20), 123 (12), 110 (100).

(1*R,2*S**)-1-Methyl-2-(2-oxopropyl)cyclopentan-1-ol Acetate (4d).** **1a** (0.096 g, 0.86 mmol) was cyclized and trapped with acetic anhydride (5 equiv, 6 h at 25 °C), yield 0.145 g (85%), bp 80 °C (0.05 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (dd, J = 15.9, 3.6 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.17 (dd, J = 15.9, 10.5 Hz, 1 H), 2.08 (s, 3 H), 1.95–1.79 (m, 3 H), 1.87 (s, 3 H), 1.71–1.44 (m, 2 H), 1.26 (s, 3 H), 1.06–0.92 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.08, 170.39, 88.75, 44.59, 44.02, 38.03, 29.87, 28.61, 21.93, 20.78, 19.20. IR (CCl_4): 2948, 1732, 1710 cm^{-1}. HRMS calcd for $C_{11}H_{18}O_3$: 198.1256, found 198.1248. LRMS (EI) m/e: 198 (2), 138 (100), 113 (62), 95 (90), 81 (67), 80 (51), 71 (51).

(1*R,2*S**)-1-(2-Hydroxy-2-methylcyclopent-1-yl)-2-propanone (4e).** **1a** (0.093 g, 0.83 mmol) was cyclized and trapped with acetic anhydride (2 equiv, 5 min at 0 °C) to yield **4e** (0.096 g, 74%). In addition, a 12% yield of **4d** was isolated, bp 80 °C (0.05 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 3.34 (br s, 1 H), 2.54–2.38 (m, 2 H), 2.18–2.10 (m, 1 H), 2.09 (s, 3 H), 1.89–1.42 (m, 5 H), 1.16–1.02 (m, 1 H), 0.99 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.55, 78.85, 45.52, 44.85, 40.96, 30.27, 29.89, 23.15, 20.70. IR (CCl_4): 3424, 2948, 1704 cm^{-1}. HRMS calcd for $C_9H_{16}O_2$: 156.1150, found 156.1140. LRMS (EI) m/e: 156 (1), 138 (23), 113 (64), 95 (35), 71 (100).

(1*R,2*S**)-2-(Hydroxymethyl)-1-methylcyclopentan-1-ol (4f).** **1a** (0.102 g, 0.91 mmol), yield 0.082 g (69%) as a 15:1 mixture of diastereomers, bp 90 °C (0.05 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 3.64–3.56 (m, 2 H), 2.84 (br s, 2 H), 2.12–1.98 (m, 1 H), 1.82–1.46 (m, 5 H), 1.19 (s, 3 H), 1.18–1.08 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): (major) δ 80.41, 63.64, 50.62, 41.03, 25.69, 22.10, 20.25; (minor) δ 80.56, 50.23, 41.09, 29.33, 29.00, 22.61. IR (CCl_4): 3424, 2948 cm^{-1}. HRMS calcd for $C_7H_{14}O_2$: 131.1072 (M + 1), found 131.1064. LRMS (EI) m/e: 115 (9), 112 (35), 97 (68), 58 (100).

(1*R,2*S**)-2-[2-(*N*,*N*-Dimethylamino)ethyl]-1-methylcyclopentan-1-ol (4g).** **1a** (0.109 g, 0.97 mmol), yield 0.121 g (73%), bp 95 °C (0.05 mmHg). ^1H NMR (300 MHz, $CDCl_3$): δ 2.34–2.20 (m, 2 H), 2.17 (s, 6 H), 1.74–1.36 (m, 10 H), 1.03 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.00, 59.89, 50.99, 45.11, 40.79, 30.24, 26.81, 22.52, 19.63. IR (CCl_4): 3220, 2937, 1534 cm^{-1}. HRMS calcd for $C_{10}H_{21}NO$: 171.1623, found 171.1608.

(1*R,2*S**)-2-(2-Methyl-2-hydroxycyclopent-1-yl)acetic Acid (4h).** **1a** (0.096 g, 0.86 mmol) yield 0.089 g (65%), mp 65–67 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (bs, 2 H), 2.44 (dd, J = 16.1, 7.8 Hz, 1 H), 2.27 (dd, J = 16.1, 6.8 Hz, 1 H), 2.32–2.20 (m, 1 H), 1.98–1.62 (m, 6 H), 1.12 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.78, 79.88, 45.85, 40.70, 34.91, 30.03, 22.68, 20.31. IR (CCl_4): 3401, 2959, 1704, 1540 cm^{-1}. HRMS calcd for $C_8H_{14}O_3$: 158.0943, found 158.0927. LRMS (EI) m/e: 143 (4), 140 (33), 125 (40), 112 (77), 111 (41), 98 (79), 97 (69), 71 (100).

High R_f Dimer. **1f** (0.080 g, 0.526 mmol) in 3 mL of THF (0.18 M) was added to 1.315 mmol of SmI_2 in 9 mL of THF and 1.5 mL of HMPA. Usual workup and flash chromatography afforded 0.031 g of the high R_f diastereomer and 0.030 g of the low R_f diastereomer. Combined yield 0.061 g (76%), mp 187–188 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.42 (br s, 2 H), 1.88–0.99 (m, 32 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.39, 49.49, 45.00, 27.70, 27.26, 26.80, 23.97, 23.33, 21.05, 20.30. IR (CCl_4): 3419, 2928, 2856 cm^{-1}. HRMS calcd for $C_{20}H_{34}O_2$: 288.2453 (M – H_2O), found 288.2455.

Low R_f Dimer. Mp 144–146 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.90–1.06 (m, 34 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.33, 51.18, 44.90, 27.95, 27.61, 26.44, 23.97, 23.36, 21.10, 20.24. IR (CCl_4): 3407, 2916, 2856 cm^{-1}. HRMS calcd for $C_{20}H_{34}O_2$: 306.2559, found 306.2534.

Table III General Procedure. Following the general procedure for cyclization of olefinic ketones **1**, substrates **1d**, **1b**, and **1k** were treated under the provisions outlined in Table III. Usual workup followed by Kugelrohr distillation afforded the products reported as determined by fused silica capillary GC, ^1H NMR, and ^{13}C NMR analyses.

Acknowledgment. This work was carried out with generous support from the National Institutes of Health. We would like to thank Professor Cortlandt Pierpont for valuable discussions.

Supplementary Material Available: Proton and carbon NMR of new compounds (47 pages). Ordering information is given on any current masthead page.

New Type of Cyclization of α,β,χ,ψ-Unsaturated Dioic Acid Esters through Tandem Conjugate Additions by Using Lithium *N*-Benzyl-*N*-(trimethylsilyl)amide as a Nitrogen Nucleophile

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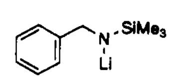
Received October 10, 1991

Treatment of dimethyl (2*E*,6*E*)-2,6-octadienedioate with lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) gave 5-*exo-trig* ring closure products, methyl 3-(*N*-benzylamino)-2-(methoxycarbonyl)cyclopentane-1-acetates, through tandem conjugate additions. The related 6-*exo-trig* cyclization proceeded stereoselectively to give ethyl *c*-3-(*N*-benzylamino)-*t*-2-(ethoxycarbonyl)cyclohexane-1-acetate. In contrast with the 5- and 6-*exo-trig* cyclization, no 7-*exo-trig* cyclization occurred. The 5-*exo-trig* cyclization products were converted into 2-(methoxycarbonyl)-2-cyclopentene-1-carboxylic acid methyl ester in an excellent yield. 5-*exo-trig* cyclization of the unsymmetrical dienedioate consisting of crotonate and (*E*)-2-methyl-2-butenoate units proceeded regioselectively through conjugate addition of LSA to the crotonate part. Similar regioselectively was observed in the case of 5-*exo-trig* cyclization of the dienedioate possessing crotonate and (*E*)-3-methyl-2-pentenoate units. Total syntheses of the physiologically active cyclopentane monoterpenes (±)-dihydronepetalactone and (±)-isohydronepetalactone has been accomplished by this cyclization strategy. In addition, it has been demonstrated that LSA is a more efficient nitrogen nucleophile than LDA to cyclize ω-halo-α,β-unsaturated esters.

When a crotonic acid ester is treated with a metal amide derived from a secondary amine, the reactions expected are (1) deprotonation of the γ-position to give the dienolate, (2) conjugate addition to give the β-amino acid ester, and (3) carboxamide formation. Recently, we have reported that lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) is an excellent nucleophile adding only in a 1,4-manner to crotonate derivatives.[2] Furthermore, the



(LSA)

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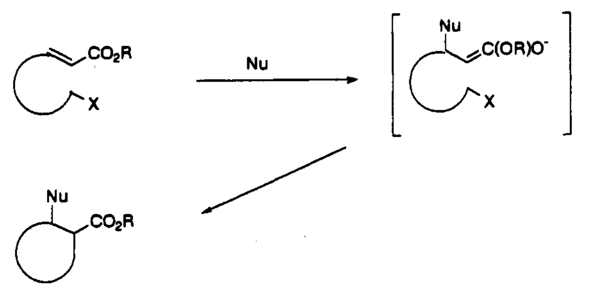
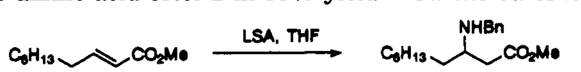
Scheme I



conjugate addition gave the Z-enolate of the β-amino acid ester selectively, and the resulting enolate could be used for intermolecular carbon–carbon bond formation.[3] For instance, a reaction with iodoalkanes gave α-alkyl-β-amino acid esters which can be transformed into β-lactams and (E)-α,β-dialkyl enoates.[2] Aldol reactions of the Z-enolate with aldehydes proceeded to give *anti,syn*-β-amino-β′-hydroxy acid esters mainly.[3] Our next interest was an application of this enolate formation to intramolecular C–C bond formation. Intramolecular alkylation of the enolates generated by conjugate addition of carbon, nitrogen, and sulfur nucleophiles to ω-halo-α,β-unsaturated esters (Scheme I) has already been investigated.[4] We report here a new entry for cyclization by means of tandem conjugate additions of α,β,χ,ψ-unsaturated dioic acid esters initiated by LSA and related reactions (Scheme II).[5]

Results and Discussion

Before attempting cyclization, we have investigated the geometrical requirements for the conjugate addition of LSA to an α,β-unsaturated ester. Reaction of methyl (E)-2-decenoate (1)[6] with LSA in THF at −78 °C gave β-amino acid ester 2 in 86% yield. On the other hand,

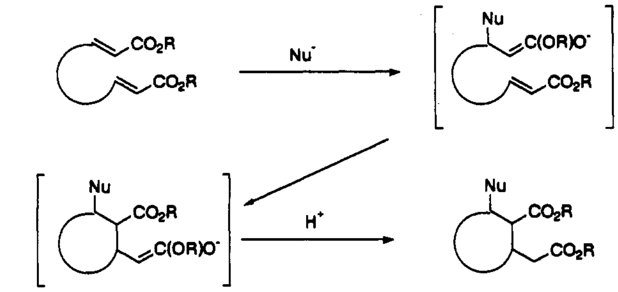


1 2 (1)

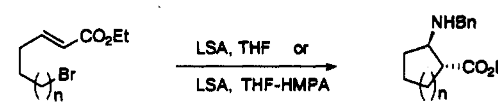
3 4 (2)

treatment of the Z-isomer of 1 (3)[6] with LSA under the same conditions gave deconjugated ester 4[7] in excellent yield. The ^{1}H-NMR spectrum of the reaction mixture derived from 1 showed the absence of deconjugated ester 4. Thus, an *E-geometry* for the α,β-unsaturated ester appears indispensable for this type of conjugate addition.

Scheme II



Cyclization Based on Tandem Conjugate Addition–Intramolecular Alkylation. LDA had already been employed as a nitrogen nucleophile for the cyclization shown in Scheme I.[4d] On the basis of our previous studies,[2] LSA seemed to be a more efficient initiator than LDA for the cyclization. In fact, a reaction of ω-bromo ester 5[8] with LSA in THF proceeded cleanly to give *trans*-2-aminocyclopentanecarboxylate 6 in 97% yield (eq 3). When



(3)

5 n = 1 6 n = 1
7 n = 2 8 n = 2
9 n = 3 10 n = 3

tandem conjugate addition–intramolecular alkylation of ω-bromo ester 7 with LSA was carried out in THF, *trans*-2-aminocyclohexanecarboxylate 8 was obtained in 67% yield. A similar treatment of 7 with LSA in THF followed by addition of HMPA afforded 8 in 79% yield. *trans*-2-Aminocycloheptanecarboxylate 10 was derived in 73% yield as a single product from the reaction of ω-iodo ester 9[9] and LSA in the presence of HMPA.

The stereostructures of these carbocycles were assigned on the basis of their ^{1}H-NMR spectra.[10] Thus, LSA is a useful nitrogen nucleophile for 5-, 6-, and 7-*tet*-cyclizations based on tandem conjugate addition–intramolecular alkylation that results in the thermodynamically more stable stereoisomer selectively.

Cyclization Based on Tandem Conjugate Additions. Because of the highly chemoselective nature of LSA, we expected that the enolate generated by 1,4-addition of the amide to one of the enoates of an (E,E)-α,β,χ,ψ-unsaturated dioic acid ester should add intramolecularly to the other enoate as shown in Scheme II.[11] Reaction of dienedioate 11[12] and LSA in THF at −78 °C gave cyclopentanecarboxylates 12 in 92% yield as a 7:3 stereoisomeric mixture. After many unsuccessful attempts to separate the stereoisomers, amino esters 12 were convergently transformed into cyclopentenecarboxylate 13[13] in 91% yield by treatment with iodomethane and K_2CO_3 in methanol. The ^{1}H-NMR spectrum of 12 suggests that the major component is methyl *c*-3-(N-benzylamino)-*t*-2-(methoxycarbonyl)cyclopentane-1-acetate.

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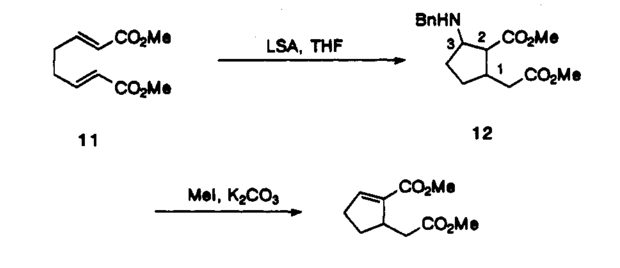
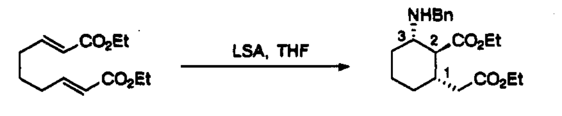
(13) Kuritani, H.; Takaoka, Y.; Shingu, K. *J. Org. Chem.* **1979**, *44*, 452.

Scheme III



11 12 13

Cyclization of homologous dienedioate 14[14] proceeded cleanly to give 15 as the sole product in 93% yield. In contrast, no cyclization products were obtained from the higher homologue 16[14] by treatment with LSA under similar conditions. Now it is clear that we can use LSA as



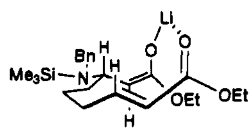
(4)

14 15

(5)

16 17

an initiator for the 5- and 6-*exo-trig* cyclizations. The stereoselective formation of 15 is rationalized to proceed through a transition state with synclinal arrangement of the enolate double bond and the carbon–carbon double bond of the enoate part such as 18.



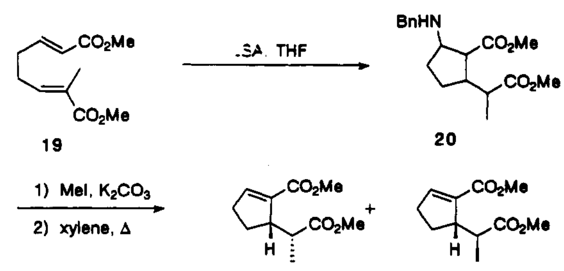
18

The cyclization of an unsymmetrical dienedioate by this type tandem conjugate addition was also investigated. Cyclopentenecarboxylate 13 and related compounds seemed to be candidates for synthetic precursors of cyclopenta[*c*]pyran monoterpenes. Therefore, we focused our attention on unsymmetrical dienedioates for 5-*exo-trig* cyclizations.

Dienedioate 19[15] consists of crotonate and (*E*)-2-methyl-2-butenoate units. Reaction of 19 with LSA at −78 °C gave a complex mixture of cyclopentanecarboxylates 20 (Scheme IV). Successive treatment of the mixture with iodomethane in the presence of K_2CO_3 and then with silica gel in boiling xylene gave a 72:28 mixture of unsaturated diesters 21 and 22 in 60% yield from 19. Thus, LSA adds highly regioselectively to 19 in a 1,4-manner, and the reactivity of the (*E*)-2-methyl-2-butenoate part is less than that of the crotonate portion. This reflects the increased electron density of the β-position due to the α-methyl group. The ratio of 21 to 22 is established at the final stage of the transformation, namely by protonation of the cyclized enolates.

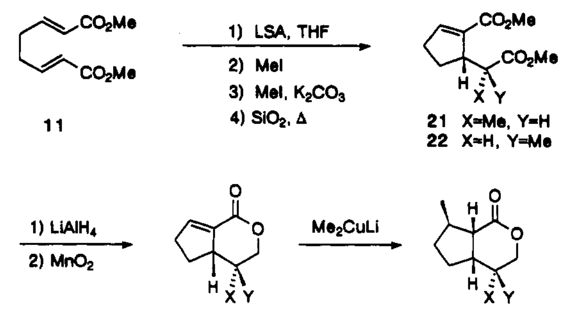
Unsymmetrical dienedioate 23 possesses crotonate and (*E*)-3-methyl-2-butenoate units. If conjugate addition of

Scheme IV



19 20 21 22

Scheme V



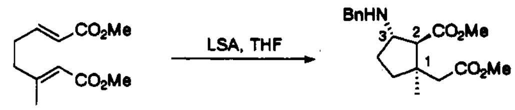
11

21 X=Me, Y=H
22 X=H, Y=Me

26 X=Me, Y=H
27 X=H, Y=Me

28 X=Me, Y=H
29 X=H, Y=Me

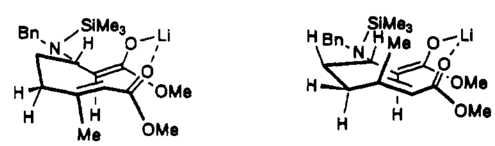
LSA to the crotonate unit proceeds more rapidly than deprotonation by LSA from the methyl group, we should expect 5-*exo-trig* cyclization. In fact, cyclopentane 24 was



(6)

23 24

derived from 23 in 28% yield. The stereochemistry of 24 was determined by ^{1}H-NMR spectroscopy. The NOE at the 2-proton upon irradiation of the 1-methyl protons, combined with the vicinal coupling constant, $J_{2,3}$ = 8.4 Hz, indicates that the 2-proton and the benzylamino group are on the same face of the ring as the 1-methyl group. Stereoselective cyclization to give 24 may proceed through transition state 25 which should be more stable than 25a.



25 25a

The stereostructure of 24 is not identical with that of the major product from 11. This means the methyl group at the β-position controls arrangement of the carbon framework for the transition state of the cyclization.

Accordingly, 5-*exo-trig* cyclization both symmetrical and unsymmetrical dienedioates can be achieved by treatment with LSA.

Total Synthesis of (±)-Dihydronepetalactone (28) and (±)-Isodihydronepetalactone (29). These cyclopentane monoterpenes are physiologically active components for the *Felidae* aminals isolated from the leaves and galls of *Actinidia polygama* Miq. and from the essential oil of *Nepeta catraria*.[16,17] Our synthetic plan is shown

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in Scheme V. Cyclopentenecarboxylates **21** and **22** are reasonable synthetic intermediates for **28** and **29**, respectively. We have already shown a synthetic route to obtain compound **21** mainly (Scheme IV). In order to obtain **22** predominantly, we attempted methylation of the cyclized enolates derived from symmetrical dienedioate **11** and LSA. After N-methylation followed by deamination, **21** and **22** were obtained in a ratio of 32:68 in 64% yield. The third route to diesters **21** and **22** is via methylation of **13**. A reaction of the enolates of **13**, derived by treatment with LDA, with iodomethane gave **21** and **22** in a 34:66 ratio in 76% yield.

Reduction of **21** with $LiAlH_4$ followed by oxidation with active manganese dioxide gave lactone **26** in 69% yield. A similar treatment of **22** gave lactone **27** in 58% yield. The stereostructures of **26** and **27** were defined on the basis of their ^{1}H-NMR spectra, thus supporting the stereochemistry of **21** and **22** assigned previously. A highly stereoselective introduction of the C-7 methyl group of **28** was carried out by treatment of **26** with dimethylcopperlithium. Similarly, **27** was converted into **29**. The spectral characteristics of **28** and **29** are identical with those of dihydronepetalactone and isodihydronepetalactone, respectively.

In conclusion, LSA is an efficient nucleophile for 5- and 6-*exo-trig* ring closures of α,β,χ,ψ-unsaturated dioic acid esters. The 5-*exo-trig* ring closures represent practical methodology for the synthesis of physiologically active cyclopentane monoterpenes.

Experimental Section

General. ^{1}H NMR spectra were measured at 270 and 600 MHz in $CDCl_3$ using TMS as the standard. THF and ether were distilled from benzophenone ketyl under argon immediately prior to use. $CHCl_3$ and benzene were distilled from P_2O_5. Butyllithium and methyllithium were obtained from the Kanto Chemical Co., Inc., and the Aldrich Chemical Co., respectively, as standardized solutions. All reactions were monitored by analytical TLC using E. Merck precoated silica gel 60F_{254} plates. Column chromatography was carried out with E. Merck silica gel 60 (70–230 mesh ASTM). Flash chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM). Semipreparative HPLC was performed using an E. Merck Hiber Prepacked column RT (250 cm × 10 mm). GC analysis was carried out on a fused silica capillary column (Shimazu CPB1-M25-025). In vacuo removal of solvent refers to the use of a rotary operating aspirator pressure and then rotary pump pressure.

Methyl 3-(*N*-Benzylamino)decanoate (2). Lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) was generated in a 50-mL two-necked round-bottomed flask equipped with a three-way stopcock and a rubber septum under argon by treatment of *N*-(trimethylsilyl)-*N*-benzylamine (0.26 mL, 1.3 mmol) with 1.62 M butyllithium (0.74 mL, 1.2 mmol) in THF (4 mL) at −78 °C for 30 min. To this solution was added a solution of **1** (184.2 mg, 1 mmol) in THF (2 mL) by means of a cannula at −78 °C. After 40 min of stirring at −78 °C, the resulting mixture was treated with methanol (2 mL). The mixture was allowed to warm to rt and then treated with 5% HCl (4 mL) for 5 min at rt in order to cleave N–Si bonds. After neutralization of the mixture by adding $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with two portions of ether. The organic layers were combined, washed with saturated brine, and dried over K_2CO_3. Removal of the solvent in vacuo gave a pale yellow liquid (351 mg). Chromatography of the liquid on silica gel (15 g, 10:1 hexane/ethyl acetate) gave **2** (260 mg, 86%) as a colorless oil: IR (CCl_4) 1740 cm^{-1}; ^{1}H NMR (270, $CDCl_3$) δ 7.34–7.21 (5 H, m, –Ph), 3.78 (2 H, broad s, –CH_2Ph), 3.67 (3 H, s, –CO_2Me), 3.02 (1 H, tt, J = 6.4 and 6.1 Hz, H-3), 2.46 (2 H, d, J = 6.1 Hz, H-2), 1.58–1.20 (13 H, m), and 0.89 (3 H, t, J = 6.5 Hz, H-10); exact mass found m/z 291.2197, calcd for $C_{18}H_{29}NO_2$ M, 291.2198. Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.29; H, 9.74; N, 4.98.

Reaction of Methyl (*Z*)-2-Decenoate (3) with LSA. Treatment of **3** (184 mg, 1 mmol) with LSA (1.2 mmol) as described for **2** gave a colorless liquid (181.4 mg, 99%). The ^{1}H-NMR spectrum of the oil indicated that it was a 95:5 mixture of methyl (*E*)-3-decenoate **4**[7] and **3**. **4**: ^{1}H-NMR (270, $CDCl_3$) δ 5.56 (1 H, dt, J = 15.0 and 5.6 Hz, H-4), 5.54 (1 H, dt, J = 15.0 and 5.6 Hz, H-3), 3.57 (3 H, s, –CO_2CH_3), 2.92 (2 H, dt, J = 5.6 and 0.8 Hz, H-2), 1.92 (2 H, td, J = 7.7 and 5.6 Hz, H-5), 1.29–1.12 (8 H, m), and 0.78 (3 H, t, J = 6.7 Hz, H-10).

Ethyl *trans*-2-(*N*-Benzylamino)cyclopentanecarboxylate (6). To a solution of LSA generated from *N*-(trimethylsilyl)-*N*-benzylamine (0.23 mL, 1.2 mmol) and 1.59 M butyllithium (0.69 mL, 1.1 mmol) in THF (4 mL) at −78 °C was added a solution of ethyl (*E*)-6-bromo-2-hexenoate (**5**)[8] (226.3 mg, 1 mmol) in THF (2 mL). After 40 min of stirring, the mixture was allowed to warm to rt and then stirred for 10 h. The resulting solution was treated with 10% Na_2CO_3 solution. The organic layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with saturated brine, and dried (K_2CO_3). Removal of the solvent in vacuo gave a liquid (392.1 mg). Chromatography of the liquid on silica gel (12 g, 10:1 hexane/ethyl acetate) gave **6** (239.4 mg, 97%) as a colorless oil: IR (CCl_4) 3420 and 1740 cm^{-1}; ^{1}H NMR (400, $CDCl_3$) δ 7.35–7.21 (5 H, m, –Ph), 4.15 (1 H, dq, J = 11.2 and 7.2 Hz, –CO_2CHHCH$_3$), 4.13 (1 H, q, J = 11.2 and 7.2 Hz, –CO_2CHHCH$_3$), 3.81 (1 H, d, J = 13.1 Hz, –NHC*H*HPh), 3.76 (1 H, d, J = 13.1 Hz, –NHC*H*HPh), 3.33 (1 H, ddd, $J_{2,1} = J_{2,3(cis)} = J_{2,3(trans)}$ = 7.4 Hz, H-2), 2.61 (1 H, ddd, $J_{1,5}$ = 8.6 and $J_{1,2} = J_{1,5}$ = 7.4 Hz, H-1), 2.15–1.95 (3 H, m), 1.86 (1 H, dddd, $J_{3,3(gem)}$ = 12.9, $J_{3,4(cis)} = J_{3,4(trans)}$ = 8.6, and $J_{3,2}$ = 7.4 Hz, H-3), 1.80–1.62 (2 H, m), 1.48 (1 H, dddd, $J_{3,3(gem)}$ = 12.6 and $J_{3,2} = J_{3,4(cis)} = J_{3,4(trans)}$ = 7.4 Hz, H-3), 1.24 (3 H, t, J = 7.2 Hz, –$CO_2CH_2CH_3$); exact mass found m/z 247.1572, calcd for $C_{15}H_{21}NO_2$ M, 247.1561. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.57; H, 8.49; 5, 5.63.

Ethyl *trans*-2-(*N*-Benzylamino)cyclohexanecarboxylate (8). (a) A reaction of ethyl (*E*)-7-bromo-2-heptenoate (**7**) (218.0 mg, 0.93 mmol) with LSA (1.1 mmol) as described for **6** gave a liquid (274.8 mg). Chromatography of the liquid on silica gel (15 g, 10:1 hexane/ethyl acetate) gave **8** (162.9 mg, 67%) as a colorless oil.

(b) To a solution of LSA (1.1 mmol) in THF (4 mL) was added a solution of **7** (190.6 mg, 0.81 mmol) in THF (2 mL) at −78 °C. After 2 h of stirring, HMPA (0.19 mL, 1.1 mmol) was added to the mixture. The mixture was allowed to warm slowly to rt, stirred overnight, and then treated with saturated NH_4Cl solution. Similar workup to that described in a followed by chromatography on silica gel (7 g, 20:1 hexane/ethyl acetate) gave **8** (167.0 mg, 79%). **8**: IR (CCl_4) 3420 and 1730 cm^{-1}; ^{1}H NMR (600, $CDCl_3$) δ 7.35–7.19 (5 H, m, –Ph), 4.15 (1 H, dq, J = 11.2 and 7.2 Hz, –CO_2CHHCH$_3$), 4.12 (1 H, dq, J = 11.2 and 7.2 Hz, –CO_2CHHCH$_3$), 3.89 (1 H, d, J = 13.2 Hz, –NHC*H*HPh), 3.72 (1 H, d, J = 13.2 Hz, –NHC*H*HPh), 2.78 (1 H, ddd, $J_{2,1(trans)} = J_{2,3(trans)}$ = 10.4, and $J_{2,3(cis)}$ = 3.6 Hz, H-2), 2.28 (1 H, ddd, $J_{1,6(trans)}$ = 12.3, $J_{1,2(trans)}$ = 10.4, and $J_{1,6(cis)}$ = 3.6 Hz), 2.14 (1 H, m, H-3), 1.98–1.91 (2 H, m), 1.81–1.67 (2 H, m), 1.49 (1 H, dddd, $J_{6,1(trans)} = J_{6,5(trans)} = J_{6,6(gem)}$ = 12.3 and $J_{6,5(cis)}$ = 3.6 Hz), 1.34–1.19 (2 H, m), 1.24 (3 H, t, J = 7.2 Hz, –$CO_2CH_2CH_3$), and 1.11 (1 H, m, H-3); exact mass found m/z 261.1733, calcd for $C_{16}H_{23}NO_2$ M, 261.1729. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.24; H, 8.71; N, 5.43.

Ethyl *trans*-2-(*N*-Benzylamino)cycloheptanecarboxylate (10). As described for **8** (b), treatment of ethyl (*E*)-8-iodo-2-octenoate (**9**)[9] (124.6 mg, 0.40 mmol) with LSA (0.48 mmol) followed by addition with HMPA (0.08 mL, 0.48 mmol) gave a liquid (192 mg). Flash chromatography of the liquid (silica gel, 25 g, 1:1 hexane/ethyl acetate) gave **10** (80.4 mg, 73%) as a colorless oil: IR (CCl_4) 3420 and 1730 cm^{-1}; ^{1}H NMR (400, $CDCl_3$) δ 7.33–7.19 (5 H, m, –Ph), 4.19 (1 H, dq, J = 10.5 and 7.2 Hz, –CO_2CHHCH$_3$), 4.09 (1 H, q, J = 10.5 and 7.2 Hz, –CO_2CHHCH$_3$), 3.84 (1 H, d, J = 13.0 Hz, –NHC*H*HPh), 3.67 (1 H, d, J = 13.0 Hz, –NHC*H*HPh), 3.01 (1 H, ddd, $J_{2,1(trans)}$ = 9.5, $J_{2,3(trans)}$ = 7.8, and $J_{2,3(cis)}$ = 3.2 Hz, H-2), 2.40 (1 H, ddd, $J_{1,2(trans)}$ = 9.5, $J_{1,7(trans)}$

(17) Syntheses of (±)-**28** and (±)-**29**: Wolinsky, J.; Euatace, E. J. *J. Org. Chem.* **1972**, *37*, 3376. Ficini, J.; d'Angelo, J. *Tetrahedron Lett.* **1976**, 6087.

= 8.2, and $J_{1,7(cis)}$ = 3.8 Hz, H-1), 1.89 (1 H, dddd, J = 14.0, 8.3, 3.2, and 1.9 Hz, H-3), 1.83–1.37 (10 H, m), and 1.22 (3 H, t, J = 7.2 Hz, $-CO_2CH_2CH_3$); exact mass found m/z 275.1883, calcd for $C_{17}H_{25}NO_2$ M, 275.1885.

Methyl 2-(Methoxycarbonyl)-2-cyclopentene-1-acetate (13). A solution of LSA (5.5 mmol) in THF (13.5 mL) was added to a stirred solution of dienedioate 11[12] (991 mg, 5 mmol) in THF (22.5 mL) at −78 °C using a stainless steel cannula. After 40 min of stirring at −78 °C, the resulting mixture was treated with methanol (2 mL). The mixture was allowed to warm to rt and then treated with 5% HCl (4 mL) for 5 min. After neutralization of the mixture by adding $NaHCO_3$ solution, the organic layer was separated and then the aqueous layer was extracted with two portions of ether. The organic layers were combined, washed with saturated brine, and dried (K_2CO_3). In vacuo removal of the solvent gave a liquid (1.888 g). Chromatography of the liquid on silica gel (57 g, 3:1–1:1 hexane/ethyl acetate) gave methyl 3-(*N*-benzylamino)-2-(methoxycarbonyl)cyclopentane-1-acetates (12) as a colorless oil (1.41 g, 92%). 12 (*c*-3-(*N*-benzylamino)-*t*-2-(methoxycarbonyl)cyclopentane-1-acetate, the major isomer): ^{1}H NMR (600, $CDCl_3$) δ 7.36–7.17 (5 H, m, –Ph), 3.77 (1 H, d, J = 13.5 Hz, –C*H*HPh), 3.72 (1 H, d, J = 13.5 Hz, –CH*H*Ph), 3.69 (3 H, s, $-CO_2Me$), 3.65 (3 H, s, $-CO_2Me$), 3.38 (1 H, ddd, $J_{3,2} = J_{3,4(cis)} = J_{3,4(trans)}$ = 7.9 Hz, H-3), 2.59 (1 H, m, H-1), 2.56 (1 H, dd, J = 15.6 and 5.8 Hz, $-CHHCO_2Me$), 2.37 (1 H, J = 15.6 and 8.0 Hz, $-CHHCO_2Me$), 2.34 (1 H, dd, $J_{2,1(trans)}$ = 9.2 and $J_{2,3}$ = 7.9 Hz, H-2), 2.00–1.90 (2 H, m, H-4 and NH), and 1.62–1.44 (3 H, m). The NOE at H-3 was observed upon irradiation of H-1. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.60; H, 7.55; N, 4.28.

To a solution of 12 (1.41 g, 4.6 mmol) in methanol (7 mL) were added K_2CO_3 (3.5 g) and iodomethane (2.3 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C. After the mixture was stirred overnight at rt, the solids were dissolved in water and the mixture was extracted with three portions of ether. The extracts were combined, washed with saturated brine, and dried (K_2CO_3). Removal of the solvent in vacuo gave an oil (943 mg). Chromatography of the oil on silica gel (10 g, 3:1 hexane/ethyl acetate) gave 13[13] as a colorless oil (831 mg, 91%). 13: IR (CCl_4) 1730 cm^{-1}; ^{1}H NMR (270, $CDCl_3$) δ 6.87 (1 H, ddd, J = 3.5, 3.5, and 2.7 Hz, H-3), 3.73 (3 H, s, $-CO_2CH_3$), 3.67 (3 H, s, $-CO_2CH_3$), 3.35 (1 H, m, H-1), 2.86 (1 H, dd, J = 14.9 and 4.8 Hz, $-CHHCO_2CH_3$), 2.56–2.41 (2 H, m), 2.34–2.16 (2 H, m), and 1.72 (1 H, m); exact mass found m/z 198.0947, calcd for $C_{10}H_{14}O_4$ M, 189.0892.

Ethyl *c*-3-(*N*-Benzylamino)-*t*-2-(ethoxycarbonyl)cyclohexane-1-acetate (15). A solution of LSA (5.4 mmol) in THF (6 mL) was added to a solution of dienedioate 14[14] (721 mg, 3 mmol) in THF (17 mL) at −78 °C by means of a stainless steel cannula. After 1 h of stirring at −78 °C, a solution of acetic acid (0.172 mL) in THF (1 mL) was added to the resulting mixture. The mixture was allowed to warm to rt and then treated with saturated sodium carbonate solution. Similar workup to that described previously followed by chromatography on silica gel (60 g, 20:1 hexane/ethyl acetate) gave 15 (957 mg, 93%) as a colorless oil: IR (CCl_4) 1730 cm^{-1}; ^{1}H NMR (400, $CDCl_3$) δ 7.32–7.19 (5 H, m, –Ph), 4.20 (1 H, dq, J = 10.5 and 7 Hz, $-CO_2CHHCH_3$), 4.17 (1 H, dq, J = 10.5 and 7 Hz, $-CO_2CHHCH_3$), 4.15 (1 H, dq, J = 18 and 7 Hz, $-CO_2CHHCH_3$), 4.10 (1 H, dq, J = 18 and 7 Hz, $-CO_2CHHCH_3$), 3.89 (1 H, d, J = 13.2 Hz, –C*H*HPh), 3.70 (1 H, d, J = 13.2 Hz, –C*H*HPh), 2.79 (1 H, ddd, $J_{3,2(trans)}$ = 11.5, $J_{3,4(trans)}$ = 10.2, and $J_{3,4(cis)}$ = 3.9 Hz, H-3), 2.31 (1 H, ddd, J = 15.6, 11.6, and 7.8 Hz, $-CHHCO_2Et$), 2.17 (1 H, m, H-4), 2.13 (1 H, m, H-1), 2.09 (1 H, m, $-CHHCO_2Et$), 2.07 (1 H, dd, $J_{2,1(trans)}$ = 9.8 and $J_{2,3(trans)}$ = 11.5 Hz, H-2), 1.85–1.74 (2 H, m), 1.33 (1 H, m), 1.25 (3 H, t, J = 7 Hz, $-CH_3$), 1.24 (3 H, t, J = 7 Hz, $-CH_3$), and 1.09–0.75 (2 H, m); exact mass found m/z 347.2118, calcd for $C_{20}H_{29}NO_4$ M, 347.2096. Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.08; H, 8.37; N, 3.97.

Reaction of Diethyl (2*E*,8*E*)-2,8-Decadienedioate (16) with LSA. A solution of LSA (1.1 mmol) was prepared from *N*-(trimethylsilyl)-*N*-benzylamine (0.234 mL, 1.2 mmol), 1.62 M butyllithium (0.687 mL), and THF (2 mL) under argon at −78 °C. The LSA solution was added to a solution of 16[14] (254 mg, 1 mmol) in THF (3 mL) at −78 °C using a cannula. After 1 h of stirring at −78 °C, the resulting mixture was treated with acetic acid (0.2 mL). The mixture was allowed to warm to rt and then treated with a saturated sodium carbonate solution. Similar workup to that described previously following by chromatography on silica gel (14 g, 20:1–1:1 hexane/ethyl acetate) gave 16 (49 mg, 20%) and diethyl (*E*)-8-(*N*-benzylamino)-2-decenedioate (17) (214 mg, 59%) as a colorless oil. 17: IR (CCl_4) 1730 cm^{-1}; ^{1}H NMR (270, $CDCl_3$) δ 7.38–7.26 (5 H, m, –Ph), 6.95 (1 H, dt, J = 14.4 and 7.0 Hz, H-3), 5.81 (1 H, dt, J = 14.4 and 1.0 Hz, H-2), 4.32 (2 H, q, J = 7.0, Hz, $-CO_2CH_2CH_3$), 4.27 (2 H, q, J = 7.0 Hz, $-CO_2CH_2CH_3$), 3.70 (2 H, s, $-CH_2Ph$), 3.16 (1 H, ddd, J = 6.2, 6.2, and 4.6 Hz, H-8), 2.60 (2 H, d, J = 6.2 Hz, H-9), 2.24–2.03 (2 H, m), 1.70–1.34 (7 H, m), 1.30 (3 H, t, J = 7.0 Hz, $-CH_3$), and 1.24 (3 H, t, J = 7.0 Hz, $-CH_3$); exact mass found m/z 361.2259, calcd for $C_{21}H_{31}NO_4$ M, 361.2253. Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64; N, 3.82. Found: C, 69.58; H, 8.42; N, 3.81.

Dimethyl (2*E*,6*E*)-2-Methyl-2,6-octadienedioate (19). Trimethyl phosphonoacetate (0.91 g, 5.0 mmol) was added slowly to a suspension of sodium hydride (40%, 200 mg, 5.0 mmol) in benzene (20 mL). The mixture was stirred for 1.5 h at rt. To the resulting mixture was added methyl 2-methyl-6-oxo-2-hexenoate[15] (360 mg, 2.3 mmol) in benzene (10 mL). After 2 h of stirring, the resulting mixture was diluted with ether, washed with water and brine, and then dried ($MgSO_4$). In vacuo removal of the solvent followed by flash chromatography on silica gel (8:1 hexane/ethyl acetate) gave a mixture of 19 and its geometrical isomers (426 mg, 87%). Diester 19 was isolated by HPLC (5:1 hexane/ethyl acetate). 19: IR (CCl_4) 1730 cm^{-1}; ^{1}H NMR (270 $CDCl_3$) δ 6.91 (1 H, dm, J = 15.4 Hz, H-6), 6.72 (1 H, m, H-3), 5.86 (1 H, dm, J = 15.4 Hz, H-7), 3.74 (3 H, s, $-CO_2CH_3$), 3.73 (3 H, s, $-CO_2CH_3$), 2.35 (4 H, m), and 1.84 (3 H, broad s, $=CCH_3$); exact mass found m/z 212.1043, calcd for $C_{11}H_{16}O_4$ M, 212.1049. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.09; H, 7.40.

Methyl (2*R)- and (2*S*)-2-[(1*S**)-2-(Methoxycarbonyl)-2-cyclopentenyl]propionates (21 and 22, Respectively).** (a) To a solution of dienedioate 19 (106 mg, 0.5 mmol) in THF (4 mL) was added a solution of LSA (1.5 mmol) in THF (5 mL) at −78 °C under argon. The mixture was stirred for 15 min and then treated with methanol. The mixture was allowed to warm to rt and treated with 1 M HCl in order to cleave N–Si bonds. After careful addition of saturated $NaHCO_3$ solution, the mixture was extracted with two portions of ether. The extracts were combined, washed with saturated brine, and dried (K_2CO_3). Removal of the solvents in vacuo followed by chromatography on silica gel (10 g, 2:1 hexane/ethyl acetate) gave amino diesters 20 as a colorless oil (137.3 mg, 86%). To a solution of 20 (130 mg, 0.4 mmol) in methanol (0.6 mL) were added K_2CO_3 (280 mg, 2 mmol) and iodomethane (0.20 mL, 3.2 mmol) at 0 °C. The mixture was stirred for 23 h at rt. The solid was dissolved in water, and the mixture was extracted with two portions of CH_2Cl_2. The extracts were combined and dried (K_2CO_3). In vacuo removal of the solvent gave a colorless oil (135 mg). To a solution of the oil in xylene (3 mL) was added silica gel (230–400 mesh, 300 mg). The mixture was heated at 170 °C (bath temperature) for 15 h under nitrogen. Flash chromatography of the resulting mixture on silica gel (10 g, hexane and then 5:1 hexane/ethyl acetate) gave a mixture of 21 and 22 (GC, 72:28) as a colorless oil (64 mg, 60% yield from 19). Diesters 21 and 22 were isolated by HPLC (5:1 hexane/ethyl acetate).

(b) To a solution of dienedioate 11 (595 mg, 3 mmol) in THF (15 mL) was added a solution of LSA (3.3 mmol) in THF (2 mL) at −78 °C under argon. After 1 h of stirring, to this solution was added iodomethane (0.84 mL, 13.5 mmol). The mixture was allowed to warm to rt and stirred for 3.5 h. The resulting solution was treated with saturated sodium carbonate solution. The organic layer was separated, and the aqueous layer was extracted with two portions of ether. The organic layers were combined, washed with saturated brine, and dried (K_2CO_3). In vacuo removal of the solvent gave amino diesters 20 as a liquid (1.137 g). N-Methylation followed by deamination similar to that described in part a gave a mixture (38:62) of 21 and 22 as a colorless oil (367 mg, 64%).

(c) A solution of LDA (1.99 M) in hexane (0.3 mL) was diluted with THF (3 mL) under argon at −78 °C. To this solution was added a solution of diester 13 (99 mg, 0.5 mmol) in THF (0.5 mL). After 15 min of stirring, to the resulting mixture was added iodomethane (0.06 mL, 1 mmol). The mixture was allowed to warm to rt and stirred for 1 h. This mixture was treated with saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with two portions of ether. The organic layers were combined, washed with saturated brine, and dried (K_2CO_3). In vacuo removal of the solvent gave a liquid (108 mg). Chromatography of the liquid on silica gel (7 g, 4:1 hexane/ethyl acetate) gave a mixture (34:66) of **21** and **22** as a colorless oil (80 mg, 76%).

21: IR (CCl_4) 1730 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 6.76 (1 H, td, $J_{3,4(cis)} = J_{3,4(trans)} = 2.7$ and $J_{3,1} = 1.6$ Hz, H-3), 3.74 (3 H, s, $-CO_2CH_3$), 3.61 (3 H, s, $-CO_2CH_3$), 3.22 (1 H, dddd, $J_{1,5(trans)} = 8.0$, $J_{1,5(cis)} = J_{1,1'} = 4.5$, $J_{1,3} = 1.6$ Hz, H-1), 3.09 (1 H, qd, $J_{1',Me} = 7.1$ and $J_{1',1} = 4.5$ Hz, $-CH(CH_3)CO_2CH_3$), 2.40 (2 H, m, H-4), 2.08 (1 H, ddt, $J_{5,5(gem)} = 13.2$, $J_{5,1(trans)} = 8.0$, and $J_{5,4(cis)} = J_{5,4(trans)} = 6.3$ Hz, H-5), 1.91 (1 H, dddd, $J_{5,5(gem)} = 13.2$, $J_{5,4(trans)} = 10.4$, and $J_{5,1(cis)} = J_{5,4(cis)} = 4.5$ Hz, H-5), and 1.15 (3 H, t, $J = 7.1$ Hz); exact mass found m/z 212.1027, calcd for $C_{11}H_{16}O_4$ M, 212.1049. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.93; H, 7.51.

22: IR (CCl_4) 1720 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 6.87 (1 H, ddd, $J_{3,4(cis)} = J_{3,4(trans)} = 2.6$ and $J_{3,1} = 1.5$ Hz, H-3), 3.74 (3 H, s, $-CO_2CH_3$), 3.69 (3 H, s, $-CO_2CH_3$), 3.55 (1 H, dddd, $J_{1,5(trans)} = 9.2$, $J_{1,5(cis)} = J_{1,1'} = 4.0$, $J_{1,3} = 1.5$ Hz, H-1), 3.13 (1 H, qd, $J_{1',Me} = 7.1$ and $J_{1',1} = 4.0$ Hz, $-CH(CH_3)CO_2CH_3$), 2.45 (2 H, m, H-4), 2.03 (1 H, dddd, $J_{5,5(gem)} = 13.1$, $J_{5,4(trans)} = 10.0$, and $J_{5,1(trans)} = 9.2$, and $J_{5,4(cis)} = 7.9$ Hz, H-5), 1.81 (1 H, dddd, $J_{5,5(gem)} = 13.1$, $J_{5,4(trans)} = 8.2$, $J_{5,4(cis)} = 6.0$ Hz, and $J_{5,1(cis)} = 4.0$ Hz, H-5), and 0.96 (3 H, d, $J = 6.9$ Hz, CH_3); exact mass found m/z 212.1027, calcd for $C_{11}H_{16}O_4$ M, 212.1049. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.99; H, 7.42%.

Dimethyl (2*E*,6*E*)-3-Methyl-2,6-octadienedioate (23). A solution of methyl (triphenylphosphoranylidene)acetate (2.53 g, 7.57 mmol) and methyl 3-methyl-6-oxo-2-hexenoate[18] (1.181 g, 7.56 mmol) in benzene (20 mL) was heated under reflux for 18 h. After removal of the solvent, the resulting sticky solid was treated with a mixture of ether (10 mL) and hexane (50 mL). In order to crystallize triphenylphosphine oxide, the mixture was allowed to stand at −20 °C overnight. The resulting mixture was filtered, and the solid was washed with ether–hexane. In vacuo removal of the solvent gave a pale yellow oil. Flash chromatography on silica gel (8:1 hexane/ethyl acetate) gave a mixture of **23** and its geometrical isomers (1.134 g, 82%). Diester **23** was isolated by HPLC (5:1 hexane/ethyl acetate). **23**: IR (CCl_4) 1730 cm^{-1}; ^1H NMR (270, $CDCl_3$) δ 6.91 (1 H, dt, $J = 15.4$ and 6.6 Hz, H-6), 5.84 (1 H, dd, $J = 15.4$ and 1.4 Hz, H-7), 5.67 (1 H, bs, H-2), 3.65 (3 H, s, $-CO_2CH_3$), 3.57 (3 H, s, $-CO_2CH_3$), 2.12–2.80 (4 H, m), and 2.16 (3 H, d, $J = 1.6$ Hz, $=CCH_3$); exact mass found m/z 212.1050, calcd for $C_{11}H_{16}O_4$ M, 212.1049. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.20; H, 7.42.

Methyl (3*S)-3-(*N*-Benzylamino)-(2*S**)-2-(methoxycarbonyl)-(1*R**)-1-methylcyclopentaneacetate (24).** To a solution of LSA (1.3 mmol) in THF (5 mL) was added a solution of dienedioate **23** (93 mg, 0.43 mmol) in THF (4 mL) at −78 °C under argon. The mixture was stirred for 30 min and then treated with methanol. The mixture was allowed to warm to rt and treated with 1 M HCl in order to cleave N–Si bonds. After careful addition of saturated $NaHCO_3$ solution, the mixture was extracted with two portions of ether. The extracts were combined, washed with saturated brine, and dried (K_2CO_3). Removal of the solvents in vacuo followed by chromatography of the resulting oil on silica gel (8 g, 3.5:1 hexane/ethyl acetate) gave **24** as a colorless oil (39 mg, 28%). **24**: IR (CCl_4) 1735 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 7.35–7.20 (5 H, m, −Ph), 3.79 (1 H, d, $J = 13.0$ Hz, $-CHHPh$), 3.73 (1 H, d, $J = 13.0$ Hz, $-CHHPh$), 3.69 (3 H, s, $-CO_2CH_3$), 3.63 (3 H, s, $-CO_2CH_3$), 3.57 (1 H, ddd, $J_{3,2(trans)} = J_{3,4(trans)} = J_{3,4(cis)} = 8.0$ Hz, H-3), 2.50 (1 H, d, $J_{2,3} = 8.0$ Hz, H-2), 2.33 (1 H, d, $J = 14.3$ Hz, $-CHHCO_2Me$), 2.26 (1 H, d, $J = 14.3$ Hz, $-CHHCO_2Me$), 2.09 (1 H, m, H-4), 1.92 (1 H, dt, $J = 12.9$ and 7.2 Hz, H-5), 1.67 (1 H, m, H-5), 1.57 (1 H, m, H-4), 1.9–1.8 (1 H, m, NH), and 1.30 (3 H, s, $-CH_3$); exact mass found m/z 319.1759, calcd for $C_{18}H_{25}NO_4$ M, 319.1784. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.71; H, 8.16; N, 4.40.

(4*R,4a*S**)-4-Methyl-4,4a,5,6-tetrahydrocyclopenta[*c*]pyran-1(3*H*)-one (26).** To a solution of diester **21** (60.4 mg, 0.28 mmol) was added a suspension of $LiAlH_4$ (150 mg) in ether (1 mL) at 0 °C. The mixture was allowed to warm to rt and then heated under reflux for 2.5 h. After being cooled to rt the mixture was treated successively with water (0.15 mL), 15% NaOH solution (0.15 mL), and water (0.45 mL) and the resulting solid filtered. Concentration of the filtrate gave a colorless oil (58.5 mg). A solution of the oil in chloroform (4 mL) was stirred with active MnO_2 (1.1 g) at rt for 15 h. The solid was filtered, and the filtrate was concentrated to give an oil (43.2 mg). Chromatography of the oil on silica gel (10 g, 10:1 hexane/ethyl acetate) gave **26** (19.1 mg, 69%) as a colorless solid: mp 53.5 °C; IR (CCl_4) 1730 and 1640 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 7.03 (1 H, dt, $J_{7,4a} = 3.2$ and $J_{7,6(cis)} = J_{7,6(trans)} = 3.2$ Hz, H-7), 4.40 (1 H, dd, $J_{3,3(gem)} = 11.4$ and $J_{3,4(cis)} = 2.6$ Hz, H-3exo), 4.25 (1 H, dd, $J_{3,3(gem)} = 11.4$ and $J_{3,4(trans)} = 2.1$ Hz, H-3endo), 3.22 (1 H, m, H-4a), 2.47 (2 H, m, H-6), 2.15 (2 H, m, H-4 and -5), 1.76 (1 H, dddd, $J_{5,5(gem)} = 12.6$ and $J_{5,4a} = J_{5,6(cis)} = J_{5,6(trans)} = 10.2$ Hz, H-5), and 0.97 (3 H, t, $J = 7.0$ Hz, $-CH_3$); exact mass found m/z 152.0842, calcd for $C_9H_{12}O_2$ M, 152.0837.

(4*S,4a*S**)-4-Methyl-4,4a,5,6-tetrahydrocyclopenta[*c*]pyran-1(3*H*)-one (27).** Conversion of diester **22** into **27** was carried as described for **26**. Diester **22** (87 mg, 0.40 mmol) was reduced by $LiAlH_4$ (150 mg). The diol (85 mg) thus obtained was oxidized by active MnO_2 (1.4 g). Chromatography of the resulting oil (45.2 mg) on silica gel (10 g, 10:1 hexane/ethyl acetate) gave **27** (35.2 mg, 58%) as colorless oil: IR (CCl_4) 1730 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 7.00 (1 H, dt, $J_{7,4a} = 2.6$ and $J_{7,6(cis)} = J_{7,6(trans)} = 2.6$ Hz, H-7), 4.29 (1 H, dd, $J_{3,3(gem)} = 11.6$ and $J_{3,4(cis)} = 4.6$ Hz, H-3endo), 3.94 (1 H, dd, $J_{3,3(gem)} = J_{3,4(trans)} = 11.6$ Hz, H-3exo), 2.56 (1 H, m, H-4a), 2.47 (2 H, m, H-6), 2.36 (1 H, m, H-5), 1.78 (1 H, ddqd, $J_{4,4a(trans)} = J_{4,3(trans)} = 11.6$, $J_{4,Me} = 6.6$, and $J_{4,3(cis)} = 4.6$ Hz, H-4), 1.56 (1 H, dddd, $J_{5,5(gem)} = 12.4$ and $J_{5,4a} = J_{5,6(cis)} = J_{5,6(trans)} = 9.9$ Hz, H-5), and 0.97 (3 H, t, $J = 6.6$ Hz, −Me); exact mass found m/z 152.0847, calcd for $C_9H_{12}O_2$ M, 152.0837.

(±)-Dihydronepetalactone, (4*S,4a*S**,7*R**,7a*S**)-4,7-Dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (28).** Dimethylcopperlithium was generated from copper(I) iodide (99 mg, 0.52 mmol) with methyllithium (1.04 mmol) in ether (3 mL) at −30 °C. To this solution was added a solution of unsaturated lactone **26** (35 mg, 0.23 mmol) in ether (1 mL) at −65 °C. The mixture was allowed to warm to 5 °C within 4 h and treated with saturated NH_4Cl solution. The ether layer was separated, and the aqueous layer was extracted with two portions of ether. The organic layers were combined, washed with water and saturated brine, and dried ($MgSO_4$). In vacuo removal of the solvent gave an oil (36 mg). Chromatography of the oil on silica gel (4 g, 3:1 hexane/ethyl acetate) gave **28** (32 mg, 83%) as a colorless oil: IR (CCl_4) 1742 cm^{-1}; ^1H NMR (400, $CDCl_3$) δ 4.09 (1 H, dd, $J_{3,3(gem)} = J_{3,4(trans)} = 10.6$ Hz, H-3endo), 4.03 (1 H, ddd, $J_{3,3(gem)} = 10.6$, $J_{3,4(trans)} = 3.8$, and $J_{3,4a} = 1.5$ Hz, H-3exo), 2.52 (1 H, m, H-4a), 2.43 (1 H, dd, $J_{7a,7(trans)} = 10.6$ and $J_{7a,4a} = 9.4$ Hz, H-7a), 2.24 (1 H, dqd, $J_{4,3(cis)} = 10.6$, $J_{4,Me} = 6.4$, $J_{4,3(cis)} = 3.8$ Hz, H-4), 2.00 (1 H, m, H-7), 1.92 (1 H, broad ddd, $J = 12.0$, 6.2, and 6.2 Hz, $W_{1/2} = 3$ Hz, H-6), 1.75 (1 H, dddd, $J = 13.2$, 12.6, 7.2, and 2.6 Hz, H-5), 1.44 (1 H, dddd, $J = 12.6$, 12.6, 10.6, and 6.2 Hz, H-5), 1.21 (3 H, d, $J = 6.4$ Hz, 7-Me), 1.18 (1 H, dddd, $J = 12.0$, 12.0, 11.8, and 6.2 Hz, H-6), and 0.90 (3 H, d, $J = 6.9$ Hz, 4-Me); ^{13}C-NMR ($CDCl_3$) δ 174.21 (s), 70.04 (t), 50.68 (d), 41.50 (d), 40.65 (d), 35.09 (t), 31.01 (d), 26.42 (t), 19.42 (q), and 13.13 (q); exact mass found m/z 168.1158, calcd for $C_{10}H_{16}O_2$ M, 168.1150.

(±)-Isodihydronepetalactone, (4*R,4a*S**,7*R**,7a*S**)-4,7-Dimethylhexahydrocyclopenta[*c*]pyran-1(3*H*)-one (29).** Introduction of a methyl group into conjugated lactone **27** was performed as described for **28**. The lactone (76 mg, 0.50 mmol) was treated with dimethylcopperlithium (1 mmol) in ether (6 mL) at −65 °C. Purification was carried out by silica gel chromatography (6 g, 3:1 hexane/ethyl acetate) to give **29** (52 mg, 90%) as a colorless oil: IR (CCl_4) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16 (1 H, dd, $J_{3,3(gem)} = 10.6$ and $J_{3,4(cis)} = 3.4$ Hz, H-3endo), 3.88 (1 H, dd, $J_{3,3(gem)} = 10.6$ and $J_{3,4(trans)} = 9.7$ Hz), 2.35 (1 H, dd, $J_{7a,4a} = 10.9$, and $J_{7a,7(trans)} = 8.7$ Hz, H-7a), 2.28 (1 H, m, H-7), 2.09 (1 H, dddd, $J_{4a,7a} = 10.1$ and $J_{4a,4} = J_{4a,5(cis)} = J_{4a,5(trans)} = 9.7$ Hz,

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H-4a) 2.03 (1 H, m, H-5) 1.87 (1 H, dddd, $J = 12.2$, 6.1, 6.1, and 2.3 Hz, H-6), 1.62 (1 H, ddqd, $J_{4,3(trans)} = J_{4,4a} = 9.7$, $J_{4,Me} = 6.9$, and $J_{4,3(cis)} = 3.4$ Hz, H-4), 1.26 (1 H, m, H-5), 1.21 (3 H, d, $J = 6.4$ Hz, 7-Me), 1.17 (1 H, m, H-5), and 1.00 (3 H, d, $J = 6.9$ Hz, 4-Me); ^{13}C-NMR ($CDCl_3$) δ 174.73 (s), 72.91 (t), 49.28 (d), 44.86 (d), 38.85 (d), 35.22 (d), 34.41 (t), 31.87 (t), 20.29 (q), and 15.76 (q); exact mass found m/z 168.1158, calcd for $C_{10}H_{16}O_2$ M, 168.1150. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.22.

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A Novel Vinyl Anion Equivalent. An Extremely Short Synthesis of 2-Substituted 2-Cycloalkenones and Prostaglandin Key Intermediates via Destannylselenenylation

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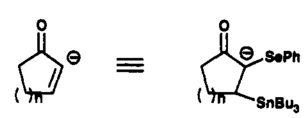
The preparation of a novel vinyl anion equivalent and a new destannylselenenylation procedure are described. The conjugate addition of (tributylstannyl)lithium to 2-(phenylseleno)-2-cycloalkenones, followed by the trapping of the resulting enolates with allylic halides, and subsequent destannylselenenylation gives 2-substituted 2-cycloalkenones in high yields, in a one-pot procedure. The destannylselenenylation can be successfully performed under a variety of conditions: treatments with fluoride, bases, Lewis acids, or silica gel as well as thermal or photochemical treatments are effective. Following the described method, chiral prostaglandin E_2 key intermediates were obtained in one pot from chiral 4-[(*tert*-butyldimethylsilyl)oxy]-2-(phenylseleno)-2-cyclopentenone.

Considerable attention has been paid to the preparation of 2-substituted 2-cycloalkenones because they can give rise to 2,3-disubstituted cycloalkanones, which are potential intermediates in many natural product syntheses.[1] For instance, a protected 4-hydroxy-2-alkyl-2-cyclopentenone is a reasonable starting point for the construction of the prostaglandin skeleton.[2] However, there are practical problems with the preparation of 2-substituted cyclopentenone intermediates. The known methods[3] for the preparation of such enones are neither simple nor versatile, and few methods for the synthesis of the chiral intermediate have been reported.[4] We now report a general procedure for the convenient synthesis of 2-substituted 2-cyclopentenones and 2-cyclohexenones using a novel vinyl anion equivalent. We also describe a very concise synthesis of protected or unprotected 4-hydroxy-2-[6-(methoxycarbonyl)-2(*Z*)-hexenyl]-2-cyclopentenones (optically active PG intermediates) starting from chiral 4-[(*tert*-butyldimethylsilyl)oxy]-2-(phenylseleno)-2-cyclopentenone.[5]

Results and Discussion

Synthesis of 2-Substituted 2-Cycloalkenones. One of the most efficient routes to 2-substituted 2-cycloalkenones is undoubtedly the direct alkylation of the vinyl anion 1. Rather than by this elusive vinyl anion, we envisioned the synthesis of these cycloalkenones via a new vinyl anion equivalent—the enolate 2, which carries adjacent stannyl and seleno groups (eq 1). The sequence



n = 1 or 2 (1)

1 2

entails (1) conjugate addition of (tributylstannyl)lithium to the 2-(phenylseleno)-2-cycloalkenone, (2) regiospecific alkylation of the resulting enolate, and (3) β-elimination of the tributylstannyl group and the phenylseleno group. One of the advantages of this method is that it can be performed in one pot. Furthermore, regiospecific forma-

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