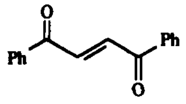
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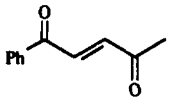
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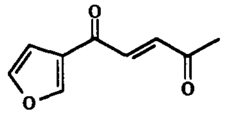
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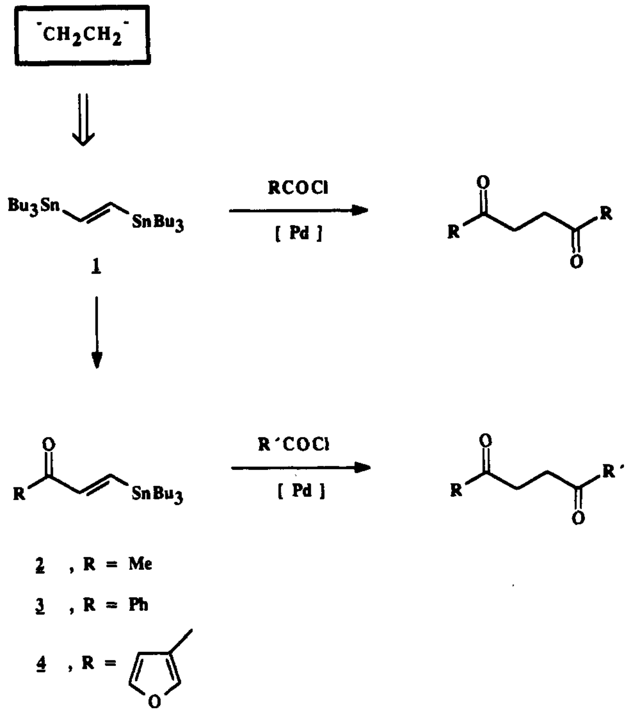
(entries 1–3) and unsymmetrical 1,4-diketones (entries 4–12) by coupling of acid chlorides with distannane 1 or β-stannyl enones 2–4. The couplings proceed in moderate to excellent yields with a variety of acid chlorides in the presence of $Pd(PPh_3)_4$ in 1,4-dioxane under reflux for 23–30 h.[17] Noteworthy, α,β-unsaturated acid chlorides (entries 1, 4, 5, and 10) yielded α,β-unsaturated-1,4-diketones in which the olefin conjugated with a single carbonyl group is not reduced under the reaction conditions.[18] This reaction was applied to the synthesis of the naturally occurring ipomeanine (14)[19] (Table I, entries 8 and 11) in a single step from readily available starting materials.

Scheme I



Noteworthy, 1,4-diphenyl-2-butene-1,4-dione (5) could be reduced to 9 by n-Bu_3SnCl, the byproduct of the coupling reaction, in the presence of several palladium catalysts (refluxing dioxane).[20] Hence, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $(PhCH_2)Pd(PPh_3)_2Cl$, $Pd(dppf)Cl_2$, $Pd(MeCN)_2Cl_2$, $Pd_2(dba)_4$ + PPh_3 (2–4 equiv), and $Pd_2(dba)_4$ + PCy_3 (2 equiv)[21] gave similar results, while $Pd_2(dba)_4$, $Ni(PPh_3)_2Cl_2$, and $Ni(CO)_2(PPh_3)_2$ were ineffective. When the reduction of 5 to 9 was performed with n-Bu_3SnCl (1–2 equiv) and $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ as the catalysts in $CDCl_3$ at 90 °C (sealed tube), a mixture of 1- and 2-butenes (cis and trans isomers)[22] and n-Bu_2SnCl_2 were also observed by ^1H and ^{13}C NMR.[23] Furthermore, almost clean conversion of n-Bu_3SnCl to n-Bu_2SnCl_2 and butenes was also observed in $CDCl_3$ at 90 °C ($Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ as the catalysts).[23a,c] These experiments indicate that n-Bu_3SnCl reacts with the palladium catalyst to give a n-butylpalladium intermediate, which undergoes β-hydride elimination to yield 1-butene and a palladium hydride. Accordingly, no reduction of 5 with Me_3SnCl was observed under the same reaction conditions. Further studies on the mechanism of this process as well as application to the synthesis of unsymmetrically substituted pyrrolidines are in progress.

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(17) General procedure: A mixture of acid chloride (1 mmol), stannane 2–4 (1 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) in 1,4-dioxane (7 mL) was heated under reflux for 23–30 h (Ar atmosphere). For the double couplings of entries 1–3, 0.5 mmol of 1 and 0.1 mmol of $Pd(PPh_3)_4$ were used. After being cooled to room temperature, the mixture was partitioned between EtOAc and aqueous $NaHCO_3$ (5%). The organic extract was washed with aqueous HCl (1.2 M), dried (Na_2SO_4), and evaporated. The residue was chromatographed to yield the 1,4-diketones. Treatment with aqueous HCl was omitted with the furyl derivatives. All compounds have been fully characterized spectroscopically. Known compounds gave satisfactory physical data. (a) 5: Lutz, R. E. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 248. (b) 6: Mayring, L.; Severin, T. *Chem. Ber.* **1981**, *114*, 3863. (c) 8: ref 4. (d) 9: ref 5c. (e) 10: Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487. (f) 11: ref 4. (g) 12: Stetter, H.; Hilboll, G.; Kuhlmann, H. *Chem. Ber.* **1979**, *112*, 84. (h) 13: ref 5b. (i) 14: ref 19. (j) 15: Schulz, G.; Gruber, P.; Steglich, W. *Chem. Ber.* **1979**, *112*, 3221. (k) 16: ref 17g.

(18) However, small amounts of 7-phenylheptane-2,5-dione were observed in the reaction of cinnamoyl chloride with stannane 2 (Table I, entry 5).

(19) Previous syntheses: (a) Kubota, T. *Tetrahedron* **1958**, *4*, 68. (b) Watanabe, E.; Imai, N.; Inomata, K.; Kinoshita, H.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3225. (c) Dimitriadis, E.; Massy-Westropp, R. A. *Phytochemistry* **1984**, *23*, 1325. (d) Liu, W. H.; Wu, H. J. *J. Chin. Chem. Soc.* **1988**, *35*, 241; *Chem. Abstr.* **1989**, *110*, 94846v.

(20) Similarly, dimethyl acetylenedicarboxylate reacts with n-Bu_3SnCl in the presence of $Pd(PPh_3)_4$ to give a mixture of dimethyl fumarate and dimethyl succinate. Maleic anhydride gave succinic anhydride under these reaction conditions.

(21) dba = dibenzylideneacetone; dppf = 1,1'-bis(diphenylphosphino)ferrocene.

(22) The 1-butene was completely isomerized to a mixture of cis- and trans-2-butenes after 12 h.

(23) (a) No n-$BuSnCl_3$ was detected in these reactions. Cleaner conversion into n-Bu_2SnCl_2 was obtained in the presence of LiCl. (b) $(n$-$Bu_3Sn)_2$ was also observed by GC-MS analysis of the reaction mixture. (c) Additionally, small amounts of uncharacterized materials were also formed in these experiments.

Asymmetric Cyclization via Tandem Conjugate Addition by Using Metal Amide Reagents. Importance of the Folded Orientation of Two Enoate Moieties

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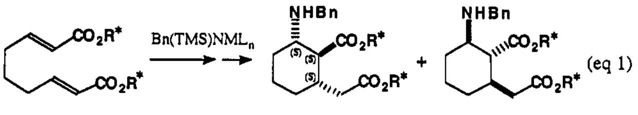
Summary: Di-(−)-menthylnona-2,7-diene-1,9-dioate (1) is converted to (−)-menthyl 3(*S*)-(*N*-benzylamino)-2(*S*)-(−)-menthoxycarbonyl)-1(*S*)-cyclohexane-1-acetate (2) with high diastereoselectivity upon treatment with the amide cuprate or zincate reagent Bn(TMS)NML$_n$ in the presence of $ZnCl_2$. The folded orientation of the two enoate moieties in 1 is essential for this high asymmetric cyclization via tandem conjugate addition.

Asymmetric carbocyclization is one of the most important processes in organic synthesis. Among several useful methods, asymmetric Diels–Alder reactions have been extensively studied, and *very elaborated chiral auxiliaries* have been used to accomplish high diastereo- and enantioselectivity.[1] We wish to report that significantly high asymmetric cyclization is realized by the tandem conjugate addition of certain metal amide reagents to nona-2,7-diene-1,9-dioic acid ester 1, in which even *a simple auxiliary* such as menthyl group produces a high diastereo- and enantioselectivity (eq 1).[2]



(eq 1)

1 *R = (-)menthyl **2** **3**

We previously reported that the reaction of $\alpha,\beta,\chi,\varphi$-unsaturated dioic acid esters with lithium *N*-benzyltrimethylsilylamide (LSA) induces ring closure via tandem conjugate additions, producing 5- and 6-membered carbocycles in good to high yields.[3] We extended this novel reaction to asymmetric carbocyclization, and the results are summarized in Table I. The use of LSA resulted in low diastereoselectivity (entry 1), whereas the conjugate addition of either the amide cuprate or zincate reagent enhanced both chemical yield and diastereoselectivity (entries 2 and 3). It should be noted that "cuprate" or "zincate" does not mean that the reagent possesses the structure $(R_2N)_2CuLi$ or $(R_2N)_3ZnLi$, respectively, but it indicates the stoichiometry of R_2N, Cu (or Zn), and Li. The amide cuprate was prepared from 2 equiv of LSA and 1 equiv of CuI in THF, and the zincate was prepared from 3 equiv of LSA and 1 equiv of $ZnCl_2$·TMEDA complex in THF. The use of bidentate chelating reagents, such as $ZnCl_2$ and $MgBr_2$, as an additive further enhanced the diastereoselectivity (entries 4–6 and 8–9), whereas a monodentate Lewis acid BF_3·OEt_2 did not exert any significant influence upon the chemical yield and selectivity (entry 7 vs 2). The absolute stereochemistry of 2 was determined by X-ray analysis (Chart I).

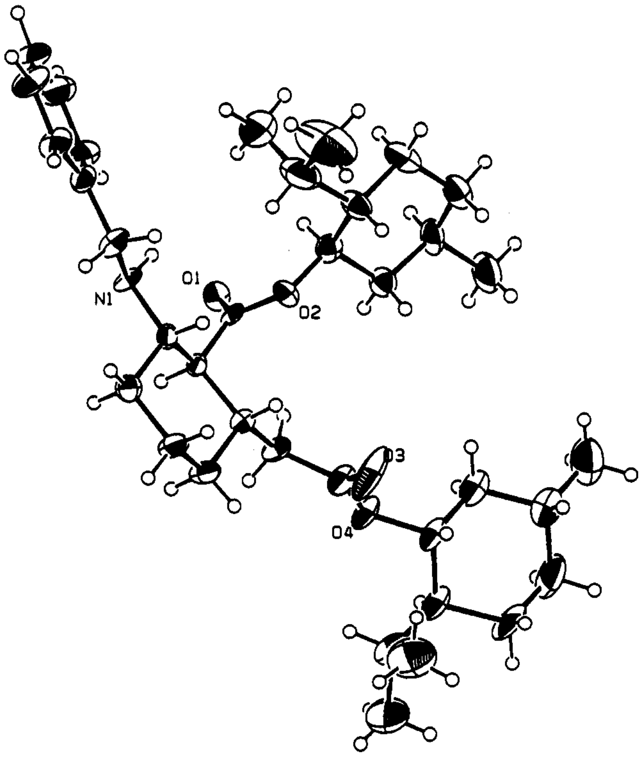
It is widely accepted that a simple chiral auxiliary such as menthyl group does not produce high diastereoselectivity in the conjugate addition of nucleophiles to enoates. To accomplish high de, elaborated auxiliaries such as 8-phenylmenthyl,[4] camphor derivatives,[5,9] pantolactone,[6] and oxazolidine[7] have been used. In fact, the zinc chloride mediated conjugate addition of the amide cuprate to menthyl monoenoates, **4a** and **b**, produced a 7:3 mixture of diastereomers **5** and **6** (eq 2). Comparison of this ratio with those of entries 2 and 4 in Table I suggested that the participation of another enoate moiety in the asymmetric conjugate addition of the amide cuprate to a double bond of 1 would cause the enhancement of the diastereoselectivity in the dienedioate system. Even in the absence of the Lewis acids, NOEs were observed between H_α at C-2 and H_β at C-7, H_β at C-3 and H_α at C-8, H_β at C-3 and H_δ at C-5, and H_α at C-8 and H_δ at C-5 (see supplementary material). The NOEs were observed not only in $CDCl_3$ but also in THF-d_8, which was used as a solvent in the asym-

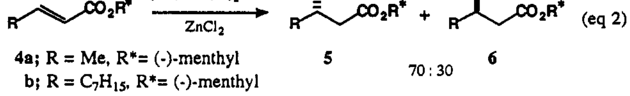
Table I. Asymmetric Cyclization of 1[a]

entry	metal amide	additive	total isolated yield, %	diastereomer ratio 2:3
1	Bn(TMS)NLi	–	70	61:39
2	[Bn(TMS)N]$_2$CuLi	–	87	77:23
3	[Bu(TMS)N]$_3$ZnLi	–	85	75:25
4	[Bn(TMS)N]$_2$CuLi	$ZnCl_2$	60	87:13
5	[Bn(TMS)N]$_2$CuLi	$MgBr_2$[b]	40	95:5
6	[Bn(TMS)N]$_2$CuLi	$MgBr_2$[c]	56	91:9
7	[Bn(TMS)N]$_2$CuLi	BF_3·OEt_2	84	77:23
8	[Bn(TMS)N]$_3$ZnLi	$MgBr_2$[b]	50	85:15
9	[Bn(TMS)N]$_3$ZnLi	$MgBr_2$[c]	77	83:17

[a] Excess amounts of the amide reagent (3–9 equiv) were used. The diastereomer ratios were determined by ^1H NMR spectra. [b] Commercially available $MgBr_2$ was crystallized from EtOH: *Purification of Lab. Chemicals*; Perrin, D. D., Armarego, W. L. F., Eds.; Pergamon: New York, 1988; p 331. [c] The $MgBr_2$ was prepared in situ from the reaction of 1,2-dibromoethane with Mg in ether at 0 °C.

Chart I. X-ray Analysis of 2





(eq 2)

4a; R = Me, R*= (-)-menthyl
b; R = C_7H_{15}, R*= (-)-menthyl

5 70 : 30 **6**

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[1] Review articles: Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 7, Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.

[2] To the best of our knowledge, only one example is known concerning the asymmetric cyclization via tandem conjugate addition to $\alpha,\beta,\chi,\varphi$-unsaturated dioic acid esters: Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533. Cyclopentane frameworks can be prepared with very high diastereoselectivity.

[3] Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 113; *J. Org. Chem.* **1992**, *57*, 3139.

[4] Whitesell, J. K.; Yaser, H. K. *J. Am. Chem. Soc.* **1991**, *113*, 3526. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

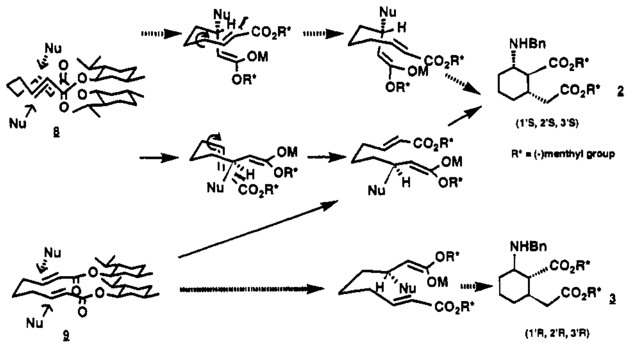
[5] For a review: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. Helmchen, G.; Wegner, G. *Tetrahedron Lett.* **1985**, *26*, 6051.

[6] Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.

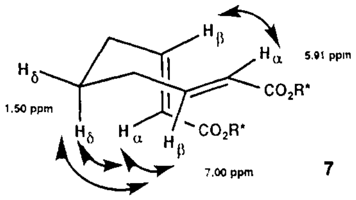
[7] Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 318.

[8] Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087.

Scheme I. Transition-State Geometries for the Formation of 2 and 3



metric cyclization. Accordingly, the diendioate 1 adopts a folded conformation (7) in solution, instead of a



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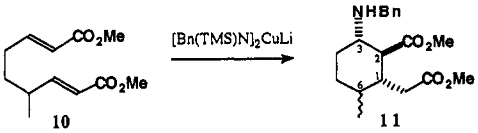
straightened structure. The bidentate Lewis acids such as $ZnCl_2$ and $MgBr_2$ chelate two oxygen atoms of the enoate groups, assisting 1 to take the folded structure. Boron trifluoride etherate, a monodentate Lewis acid, does not participate to fold the framework of the nonadiendioic acid ester.

Diastereoselective formation of 2 is accounted for by the nucleophilic addition to 8 (Scheme I). The addition to either double bond of 8 produces 2. The result of NOE experiments is in good agreement with this geometry. The addition to 9 from the direction shown by a solid arrow produces 2, although the addition from the direction indicated by a dotted arrow affords 3. Accordingly, the tandem conjugate addition to 9 would result in low diastereoselectivity. Furthermore, the geometry 9 is inconsistent with the observation obtained in the NOE measurement. It should be noted that the enoate geometry of 8 is a (*S*)-cis form whereas a (*S*)-trans form is involved in the conjugate addition of organocopper·BF_3 reagents to 8-phenylmenthyl crotonate.[9]

We are now in a position to control the stereochemistries of three contiguous chiral centers of 2 via the tandem conjugate addition. We next tested whether or not the stereochemistries of four contiguous chiral centers can be controlled. The conjugate addition of $[Bn(TMS)N]_2CuLi$ to 10 in THF at −100 °C gave 11 as a 1:1 mixture of two diastereomers in 82% yield. The stereocontrol at the C-6 position of 11 was not accomplished. However, it is clear that very high regiocontrol is achieved; the conjugate addition took place exclusively at the less hindered double bond of **10**.



The conjugate addition of the amide cuprate reagent to 1 is as follows. A 50-mL flame-dried, two-necked, round-bottom flask, equipped with a magnetic stirring bar, was fitted with a rubber septum and a three-way stopcock under argon. The apparatus was charged with 16 mg (0.62 mmol) of magnesium and 0.5 mL of ether. The suspension was cooled to 0 °C, and 51 μL (0.6 mmol) of 1,2-dibromethane was added. The mixture was stirred for 20 h. In a 50-mL flask was placed 92 mg (0.2 mmol) of 1 dissolved in 2 mL of ether at −78 °C. The magnesium bromide suspension was transferred to this dienedioate solution via a stainless steel cannula, and the mixture was stirred for 1.5 h. Another 50-mL flask was charged with 3 mL of THF and 0.75 mL (3.82 mmol) of *N*-(trimethylsilyl)benzylamine. The mixture was cooled to −78 °C, and *n*-BuLi (2.25 mL, 1.65 M hexane solution, 3.72 mmol) was added dropwise. The solution was stirred for 40 min. The lithium amide reagent was transferred to a suspension of CuI (360 mg, 1.87 mmol) in THF (3 mL) at −78 °C via a stainless steel cannula. After being stirred at −78 °C for 1.5 h, the copper amide suspension was cooled to −100 °C. The dienedioate solution was transferred to the copper amide suspension via a stainless steel cannula. After being stirred at −100 °C for 40 min, the reaction mixture was quenched by the addition of 2 mL of methanol. The mixture was allowed to warm to room temperature and then treated with 1 N hydrochloric acid solution, with saturated aqueous sodium bicarbonate solution, and with saturated aqueous NH_4Cl/NH_4OH. The organic layer was separated, and the aqueous layer was extracted with two portions of ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, with aqueous NH_4Cl solution, and with brine. The organic layer was dried with anhydrous sodium sulfate. Concentration and purification with column chromatography on SiO_2 (15 g, hexane:ethyl acetate = 10:1) gave 2 and its diastereomer (44 mg, 40%) as a colorless oil.

Supplementary Material Available: Synthetic methods, characterization data, and NMR spectra (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) Oppolzer, W.; Löher, H. J. *Helv. Chim. Acta* 1981, *64*, 2808.