Allylic chlorination gave Z-dienyl chloride 10 that reacted with lithium diphenylphosphide[15] and then with hydrogen peroxide to form allylic phosphine oxide 11. Thus in 11 steps and in 32% overall yield, easily prepared 3-bromo-2-pyrone has been transformed into an immediate precursor of 1α,2α,25-trihydroxyvitamin $D_3$, a new analogue of vitamin $D_3$.

Important aspects of this report include the following: (1) discovery that 3-bromo-2-pyrone can be coaxed into effective inverse-electron-demand cycloaddition with an electron-rich dienophile under sufficiently mild thermal conditions to prevent loss of $CO_2$ from the initial bicycloadduct; (2) use of easily prepared 3-bromo-2-pyrone instead of less easily prepared 3-(tolylsulfonyl)-2-pyrone as an important practical improvement of this cycloaddition methodology;[6] (3) use of a new sulfinyl ortho ester for one-flask, regiospecific conversion of complex allylic alcohol 7 into 2-carbon-extended conjugated dienoate ester 8; and (4) demonstration that silyl ether protection in contrast to alkyl ether protection can effectively prevent ether oxygen–Lewis acid coordination (e.g. Z-8 → 9).

Continuing efforts are being directed at (1) preparation of enantiomerically pure allylic phosphine oxide 11; (2) conversion of 11 into 1α,2α,25-trihydroxyvitamin $D_3$ via Lythgoe coupling;[14,16] and (3) biological evaluation of this new vitamin $D_3$ derivative. Results of these efforts will be reported in due course.

**Acknowledgment.** We thank the NIH (GM-30052) for generous financial support and Professor Jacqueline Seyden-Penne (Orsay, France) for first bringing to our attention the difference in Lewis acid coordinating ability of silyl vs alkyl ethers.

**Supplementary Material Available:** Characterization of compounds 3–11 (5 pages). Ordering information is given on any current masthead page.

# Decarboxylative Cyclization of Allylic Cyclic Carbamates: Applications to the Total Synthesis of (−)-Codonopsine[1]

Chia-Lin J. Wang*,† and Joseph C. Calabrese‡

*Du Pont Merck Pharmaceutical Co., Experimental Station, P.O. Box 80353, Wilmington, Delaware 19880-0353, and Du Pont Co., Central Research and Development Department, Experimental Station, Wilmington, Delaware 19880-0228*

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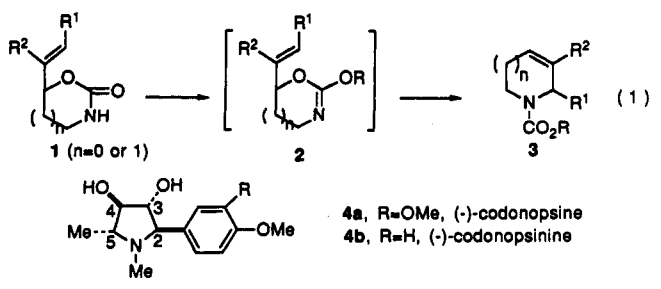
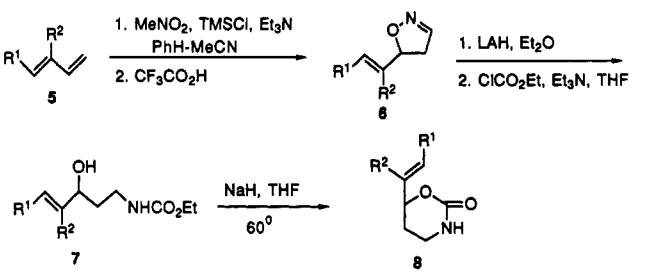
*Summary:* Decarboxylative cyclization of allylic cyclic carbamates 1 leading to 2-substituted Δ³-piperidines and -pyrrolidines, as well as its application to the total synthesis of (−)-codonopsine, is described.

2-Alkyl-Δ³-piperidines and -pyrrolidines are useful intermediates in the synthesis of various alkaloids.[2] None of the methods for synthesis of these compounds, however, are suitable for the synthesis of 2-aryl-Δ³-pyrrolidines. In a project directed toward the synthesis of (−)-codonopsine (**4a**), a natural product[3] that possesses hypotensive activity with no effect on the central nervous system,[4] we needed a 2-aryl-Δ³-pyrrolidine as a key intermediate. A general entry to both 2-aryl- or alkyl-substituted Δ³-pyrrolidines and -piperidines was desired for the synthesis not only of (−)-codonopsine but also of other alkaloids such as pumiliotoxin C.[5] Since the Claisen rearrangements of lactonic (silyl) enolates[6] and acyclic allylic imidates[7] to functionalized cycloalkenes and amides have been fruitful areas of organic synthesis, we initiated a program to study whether allylic cyclic carbamates 1 undergo similar rearrangement to 3 through intermediate 2 (eq 1). Herein we report our preliminary results and an application to the first total synthesis of natural (−)-codonopsine.

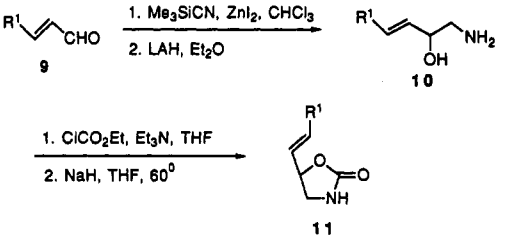



†Du Pont Merck Pharmaceutical Co.
‡Du Pont Co.

**Scheme I**




**Scheme II**

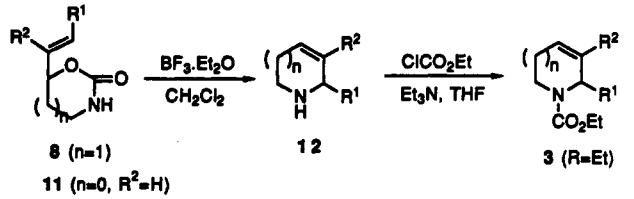



The synthesis of compounds 1 ($n$ = 1) is shown in Scheme I. Addition of trimethylsilyl ester of *aci*-nitro-

(1) Contribution No. 91-P9 from Du Pont Merck Pharmaceutical Co.
(2) (a) Shono, T.; Terauchi, J.; Ohki, Y.; Matsumura, Y. *Tetrahedron Lett.* **1990**, *31*, 6385. (b) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1990**, *55*, 4668. (c) Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711. (d) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193.
(3) (a) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1969**, *5*, 30; *Chem. Abstr.* **1969**, *71*, 13245z. (b) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Ibid.* **1969**, *5*, 607; *Chem. Abstr.* **1970**, *73*, 25712d. (c) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Ibid.* **1969**, *5*, 606; *Chem. Abstr.* **1970**, *73*, 15050x. (d) Matkhalikova, S. F.; Malikov, V. M.; Yagudaev, M. R.; Yunusov, S. Yu. *Ibid.* **1971**, *7*, 210; *Chem. Abstr.* **1971**, *75*, 36409c. (e) Yagudaev, M. R.; Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Ibid.* **1972**, *8*, 495; *Chem. Abstr.* **1972**, *77*, 164902m. (f) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 1956.

0022-3263/91/1956-4341$02.50/0 

**Table I**




8 (n=1)
11 (n=0, $R^2$=H)
12
3 (R=Et)

| entry | $R^1$ | $R^2$ | $n$ | 3 (R = Et), yield (%) |
|---|---|---|---|---|
| 1 | Ph | H | 1 | 85 |
| 2 | $n$-$C_6H_{13}$ | $SiMe_3$ | 1 | 76 |
| 3 | $n$-$C_6H_{13}$ | H | 1 | 20 |
| 4 | 3,4-$(MeO)_2C_6H_3$ | H | 0 | 80 |
| 5 | Ph | H | 0 | 20 |
| 6 | $n$-$C_5H_{11}$ | H | 0 | 0 |

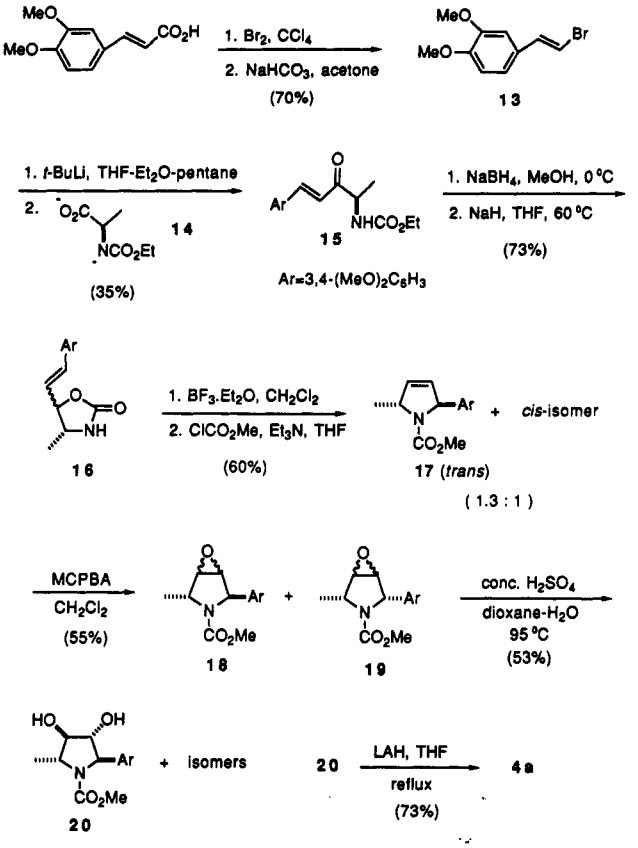
methane[8] to diene 5[9] gave 2-isoxazoline 6[10] in 70–80% yield. Treatment of 6 with $LiAlH_4$, followed by ethyl chloroformate in the presence of triethylamine, yielded ca. 50% of 7, which was converted to 8 smoothly using sodium hydride at 60 °C in 75–85% yield.

In order to prepare compounds 1 with $n$ = 0, $R^2$ = H, the aldehyde 9[11] was treated with trimethylsilyl cyanide[12] and the resulting silylated cyanohydrin was directly reduced with $LiAlH_4$ to give 80% of amino alcohol 10. Reaction of 10 with ethyl chloroformate, followed by sodium hydride, afforded 11 in 50–60% yeld (Scheme II).

The Claisen rearrangement of 8 and 11 was carried out using 1 equiv of boron trifluoride etherate in methylene chloride at room temperature[13] to give decarboxylative cyclization products 12 isolated as their ethyl carbamates (Table I). Moderately high yields (e.g. entries 1, 2, and 4) of the cyclization were obtained when $R^1$ is electron-donating or $R^2$ is a trimethylsilyl group, which can stabilize a $\beta$-carbonium ion. This observation supports the permise that a carbonium ion or ion pair is an intermediate[14] in the decarboxylative cyclization. Other Lewis acids such as zinc chloride also affected the decarboxylative cyclization, but aluminum chloride and titanium tetrachloride failed to give the desired cyclization products.

This decarboxylative cyclization provides access to various 2-substituted $\Delta^3$-piperidines or -pyrrolidines. This methodology has been used for the synthesis of (–)-codonopsine. Bromination of *trans*-3,4-dimethoxycinnamic acid, followed by decarboxylative dehydrobromination with sodium bicarbonate in refluxing acetone,[15] gave a 70% yield of (*E*)-vinyl bromide 13 (Scheme III). Treatment of 13 with *t*-BuLi[16] at –100 °C generated the vinyl anion, which was reacted with dianion 14 (prepared from *N*-(ethoxycarbonyl)-D-alanine and 2 equiv of *n*-BuLi) to afford enone 15 in 35% chromatographic yield ($[\alpha]^{20}_D$ = –38.5° ($c$ = 0.338, $CHCl_3$)).[17] Sodium borohydride reduction of 15, followed by cyclization with sodium hydride, gave a 73% yield of cyclic carbamate 16 as a cis and trans mixture in a 2:1 ratio. Decarboxylative cyclization with boron trifluoride etherate and isolation of the products as their methyl carbamates afforded 17 and the corresponding cis isomer in 60% yield in a ratio of ca. 1.3:1 as determined by $^1H$ NMR spectroscopy. The stereochemical assignments of 17 were eventually confirmed by conversion to (–)-codonopsine. The mixture was epoxidized with *m*-CPBA in methylene chloride at room temperature to afford 18 and 19 in 55% yield and the recovered starting material (15%). The epoxides were then hydrolyzed with concd $H_2SO_4$ in dioxane–water at 95 °C to give a chromatographically separable mixture of diol 20 (30%) and other isomers (23%). Finally, $LiAlH_4$ reduction of 20 in refluxing THF provided (–)-codonopsine as a white crystalline compound in 73% yield, mp 148–150 °C (lit.[3a] mp 150–151 °C); $[\alpha]^{20}_D$ = –14° ($c$ = 0.16, MeOH) (lit.[3a] $[\alpha]^{20}_D$ = –16° ($c$ = 0.84, MeOH)). The $^1H$ NMR and MS spectral data were also consistent with those reported in the literature.[3e] X-ray crystallographic analysis of 4a showed the relative stereochemistry as indicated. Thus, this work has confirmed the absolute configuration of natural codonop-

**Scheme III**




(4) Khanov, M. T.; Sultanov, M. B.; Egorova, T. A. *Farmakol. Alkaloidov Serdech. Glikoyidov.* **1971**, 210; *Chem. Abstr.* **1972**, *77*, 135091r.
(5) Lebel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363 and references cited therein.
(6) (a) Buchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126. (b) Ireland, R. E.; Muller, R. H. *Ibid.* **1972**, *94*, 5897. (c) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *Ibid.* **1980**, *102*, 6889. (d) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (e) Angle, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1989**, *30*, 515.
(7) (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.
(8) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2247.
(9) For the synthesis of 5 ($R^1$ = $C_6H_{13}$, $R^2$ = $SiMe_3$), see: Negishi, E.-i.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 1560.
(10) All new compounds gave satisfactory $^1H$ NMR, IR, and MS spectra.
(11) Compound 9 [$R^1$ = 3,4-$(MeO)_2C_6H_3$] was prepared from *trans*-3,4-dimethoxycinnamic acid by (1) (a) $ClCO_2Et$, $Et_3N$; (b) $NaBH_4$, $H_2O$, THF; (2) $MnO_2$, $CHCl_3$, reflux.
(12) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.
(13) A typical procedure: A solution of 8 ($R^1$ = Ph, $R^2$ = H) (500 mg, 2.46 mmol) in $CH_2Cl_2$ (20 mL) was treated with boron trifluoride etherate (0.3 mL, 2.46 mmol) at rt for 24 h. It was then washed with saturated $NaHCO_3$ solution and brine and dried ($Na_2SO_4$). The crude 12 ($R^1$ = Ph, $R^2$ = H; 415 mg) obtained was reacted with $ClCO_2Et$ (0.25 mL, 2.6 mmol) and $Et_3N$ (0.36 mL, 2.6 mmol) in THF (5 mL) at rt for 1 h. Aqueous workup, followed by chromatographic purification of the crude product, afforded 483 mg (85%) of 3 (R = Et, $R^1$ = Ph, $R^2$ = H, $n$ = 1).
(14) (a) Roberts, R. M.; Hussein, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 1950. (b) Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976.
(15) Galamb, V.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 2965.
(16) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839.
(17) Wolf, J.-P.; Pfander, H. *Helv. Chim. Acta* **1986**, *69*, 918.

sine to be 2R,3R,4R,5R as previously proposed.[3f]

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**Supplementary Material Available:** Experimental procedures, spectral data, and physical properties for compounds **6–8** ($R^1$ = Ph, $R^2$ = H), **10–11** ($R^1$ = 3,4-$(MeO)_2C_6H_3$), **13**, **15–20**, and **4a** and an X-ray ORTEP drawing and crystallographic parameters for **4a** (8 pages). Ordering information is given on any current masthead page.

# *Articles*

## About the Origin of the Chiroptical Properties of the Planar Diene Chromophore in Cyclohexylidenepropene Derivatives†

M. Clericuzio,‡,⊥ C. Rosini,§,⊥ M. Persico,⊥ and P. Salvadori*,§,⊥

*Scuola Normale Superiore, P.zza dei Cavalieri 7, 56126 Pisa, Italy, Centro CNR Macromolecule Stereordinate ed Otticamente attive, via Risorgimento 35, 56126 Pisa, Italy, and Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy*

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The circular dichroism of the lowest energy $\pi-\pi^*$ transition in cyclohexylidenepropenes (a class of s-trans dienes) has been investigated theoretically. Two calculation methods, viz. the De Voe coupled oscillators theory and a semiempirical MO–SCF method (CNDO/S), have been employed. CD signs opposite to those experimentally found by Walborsky and co-workers have been obtained for every molecule studied. A possible origin of this disagreement cannot be found in a twist of the diene chromophore on the basis of the theoretical conformational analysis (MMP2 and ab initio SCF calculations give planar diene structure); the origin of the optical activity of these compounds seems then to be an open question.

### Introduction

The origin of optical activity in the diene chromophore, in particular the circular dichroism (cd) of the lowest energy $\pi-\pi^*$ transition, has been the subject of several experimental and theoretical investigations,[1] and various chirality rules have been proposed[1] to correlate the spectral data with the molecular structure. Most of the interest has been devoted[1] to 1,3-cisoid dienes, while the transoid systems received much less attention. Only in recent years have some interesting papers by Walborsky and co-workers appeared in the literature[2-4] dealing with the synthesis, structure, and chiroptical properties of cyclohexylidene-substituted, planar s-trans butadienes. It is worth mentioning that they proposed[2] a sector rule, the planar diene rule, to correlate the sign of the long-wavelength $\pi-\pi^*$ cd transition with the absolute configuration. They also provided a qualitative interpretation[3] of the cd data of these systems on the basis of the two-group electric dipole mechanism.[5] In 1988, Walborsky, Reddy, and Brewster empirically introduced[6] a more complex sector rule, which explicitly superseded the first one. In addition, they also attempted, without success, to apply the Weigang treatment[7] to have quantitative estimation of the cd allied to lowest energy $\pi \rightarrow \pi^*$ transition of these systems. In this paper, we try to provide a *quantitative* analysis of the cd data of the previous transoid dienes employing a dynamic coupling method of calculation, the De Voe model,[8] which has been successfully used in several instances to reproduce the cd of simple symmetric chromophores perturbed by polarizable groups dissymmetrically disposed around it. This model has been described in detail elsewhere,[9] so only most important features will be presented here. A De Voe treatment of the optical properties of a chiral molecule requires a division of the molecule in a set of suitable

† This paper is dedicated to the memory of Prof. Piero Pino (1921–1989).

‡ Scuola Normale Superiore.

§ Centro CNR Macromolecole Stereordinate ed Otticamente attive.

⊥ Università di Pisa.

(1) Taking into account the large body of papers that appeared about the chiroptical properties of the diene chromophore, we only quote here those references where a general discussion of the previous literature is also reported: (a) Charney, E. *The molecule basis of optical activity: Optical Rotatory Dispersion and Circular Dichroism*; Wiley: New york, 1979. (b) Lightner, D. A.; Boumann, T. D.; Gawronsky, J. K.; Gawronska, K.; Clappuis, J. L.; Gast, B. V.; Hansen, A. T. *J. Am. Chem. Soc.* **1981**, *103*, 5314. (c) Brown, A. R.: Drake, A. F.; Kearney, F. R.; Mason, S. F.; Paquette, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 6123.

(2) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1983**, *105*, 3264. Actually, these authors also treated other cyclohexylidene-substituted systems, such as unsaturated aldehydes, ketones, and esters.

(3) Gawronsky, J. K.; Walborsky, H. M. *J. Org. Chem.* **1986**, *108*, 2863.

(4) (a) Walborsky, H. M.; Gawronska, K.; Gawronsky, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 6719. (b) Gawronsky, J. K.; Reddy, S. M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1987**, *109*, 6726.

(5) See, for instance: Mason, S. F. *Molecular Optical Activity and the Chiral Discrimination*; Cambridge University Press: Cambridge, 1982; p 42 and references therein.

(6) Walborsky, H. M.; Madhava Reddy, S.; Brewster, J. H. *J. Org. Chem.* **1988**, *53*, 4832.

(7) Weigang, O. E. *J. Am. Chem. Soc.* **1979**, *101*, 1965.

(8) De Voe, H. *J. Chem. Phys.* **1965**, *43*, 3199.

(9) (a) Zandomeneghi, M.; Rosini, C.; Salvadori, P. *Chem. Phys. Lett.* **1976**, *44*, 533. (b) Rosini, C.; Zandomeneghi, M.; Salvadori, P. *J. Chem. Soc., Dalton Trans.* **1978**, 877. (c) Zandomeneghi, M. *J. Phys. Chem.* **1979**, *83*, 2969. (d) Salvadori, P.; Bertucci, C.; Rosini, C.; Zandomeneghi, M.; Gallo, G. G.; Martinelli, E.; Ferrari, P. *J. Am. Chem. Soc.* **1981**, *103*, 5553. (e) Rosini, C.; Zandomeneghi, M. *Gazz. Chim. Ital.* **1981**, *111*, 493. (f) Zandomeneghi, M.; Rosini, C.; Drake, A. F. *J. Chem. Soc., Faraday Trans. 2* **1981**, *77*, 567. (g) Rosini, C.; Giacomelli, G.; Salvadori, P. *J. Org. Chem.* **1984**, *49*, 3394. (h) Rosini, C.; Bertucci, C.; Salvadori, P.; Zandomeneghi, M. *J. Am. Chem. Soc.* **1985**, *107*, 17.

0022-3263/91/1956-4343$02.50/0 