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Communications

Novel Synthesis of Nitrogen Heterocycles Using Zirconium-Promoted Reductive Coupling. Formal Total Synthesis of Dendrobine

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Summary: A novel synthesis of nitrogen heterocycles by means of a zirconium-promoted, intramolecular reductive coupling reaction of an enyne or a diene was developed, and the formal total synthesis of dendrobine from (−)-carvone was achieved by a short sequence of steps.

Reductive coupling of multiple bonds with transition metals is a powerful synthetic method because a new carbon–carbon bond is formed from the multiple bonds. Zirconacycles, which are easily prepared from enynes, dienes, or diynes and a low-valent zirconocene, have been especially useful intermediates for the stereocontrolled synthesis of cyclic compounds.[1-3] We now report a highly regio- and stereoselective synthesis of nitrogen heterocycles and the formal total synthesis of dendrobine using this method.

When a THF solution of cyclohexenylamine **1** and zirconocene, prepared from Cp_2ZrCl_2 and BuLi as reported by Negishi,[2b] was stirred at room temperature for 3 h and the resultant zirconacycle was hydrolyzed with 10% HCl, perhydroindole **3a** was obtained as a single isomer in 75% yield. The NOE experiment on Ha and R_2 of **3a** indicated that the *Z*-olefin was formed selectively. Since the carbon–zirconium bonds of the intermediate zirconacycle (**2**) were very reactive, substituents R_1 and R_2 could be introduced easily by treatment of **2** with various reagents. Moreover, substituents could be introduced regioselectively because each of the carbon–zirconium bonds of zirconacycle **2** could be cleaved selectively by a different reagent[4] (Table I, runs 4–7); that is, the sp^3 carbon was attacked by the first reagent, and the sp^2 carbon was then attacked by the second reagent. Perhydroindoles **3b–3g** were synthesized in one pot from cyclohexenylamine **1** in a highly stereocontrolled manner.

Table I. Reaction of 2 with Various Reagents

run	E_1^+	E_2^+	R_1	R_2	products	yields (%)
1	10% HCl		H	H	3a	75
2	10% DCl		D	D	3b	65
3	I_2		I	I	3c	25
			I	H	3d	15
4	^{t}BuNC	50% HOAc	CHO	H	3e	36
5	BnNC	50% HOAc	CHO	H	3e	52
6	CH_3CH_2COOH	10% DCl	H	D	3f	45
7	^{t}BuNC	I_2	CHO	I	3g	42

When a THF solution of zirconacycle **2** prepared from **1** was stirred under an atmosphere carbon monoxide at

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(1) (a) Yasuda, H.; Kajihara, Y.; Mashima, K.; Nagasuna, K.; Nakamura, A. *Chem. Lett.* **1981**, 671. Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N., Akita, M.; Yasuda, H.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3735. (b) Gell, K. I.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2687. (c) Buchwald, S. L.; Watson, B. T. *Ibid.* **1987**, *109*, 2544. Buchwald, S. L.; LaMaire, S. J. *Tetrahedron Lett.* **1987**, *28*, 295. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486. Buchwald, S. L.; Kreutzer, K. A.; Fisher, R. A. *Ibid.* **1990**, *112*, 4600. Buchwald, S. L.; King, S. M. *Ibid.* **1991**, *113*, 258. Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *Ibid.* **1991**, *113*, 4685. Barr, K. J.; Watson, B. T.; Buchwald, S. L. *Tetrahedron Lett.* **1991**, *32*, 5465. Fisher, R. A.; Buchwald, S. L. *Organometallics* **1990**, *9*, 871. Cuny, G. D.; Buchwald, S. L. *Ibid.* **1991**, *10*, 363. (d) Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495. Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. (e) Coles, N.; Whitby, R. J.; Blagg, J. *Synlett* **1990**, 271. (f) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. Nugent, W. A.; Thron, D. L.; Harlow, R. H. *Ibid.* **1987**, *109*, 2788. Rajanbabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *Ibid.* **1988**, *110*, 7128. Nugent, W. A.; Taber, D. F. *Ibid.* **1989**, *111*, 6435.

(2) (a) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *Ibid.* **1985**, *107*, 2568. (b) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (c) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Ibid.* **1987**, *28*, 917. (d) Negishi, E.; Swanson, D. R.; Miller, S. R. *Ibid.* **1988**, *29*, 1631. (e) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. (f) Negishi, E.; Miller, S. R. *J. Org. Chem.* **1989**, *54*, 6014. (g) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336. (h) Swanson, D. R.; Rousset, C. J.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 3521. (i) Swanson, D. R.; Negishi, E. *Organometallics* **1991**, *10*, 825.

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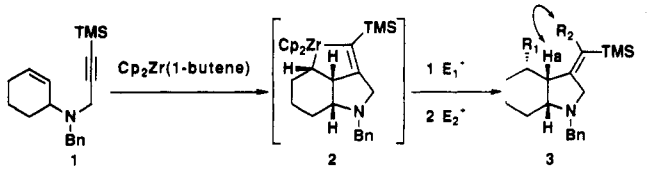
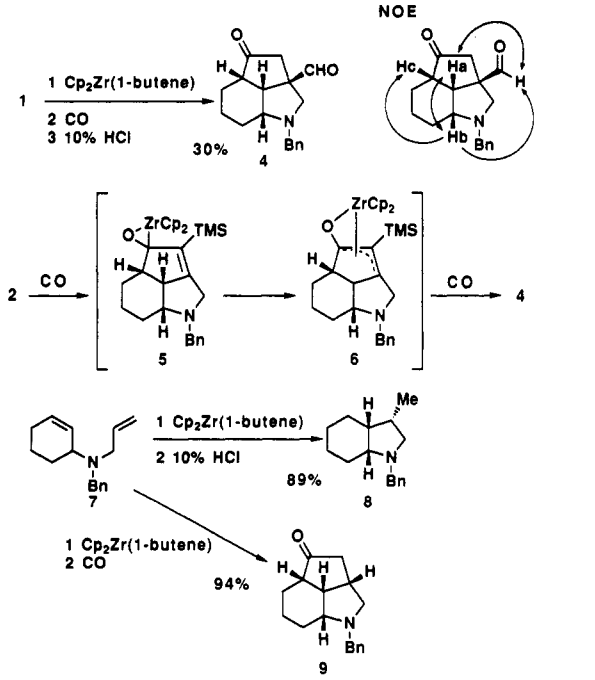
Scheme I



Scheme II



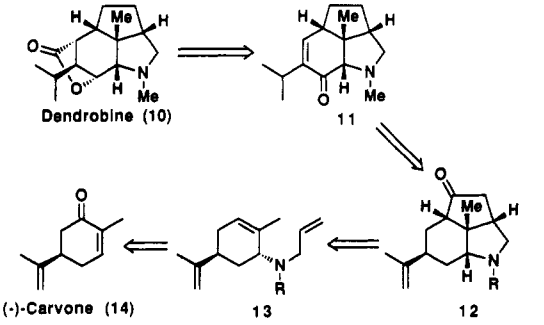
room temperature for 18 h, an unexpected product, tricyclic ketone **4**, was obtained as a single isomer in 30% yield. The structure was confirmed by spectroscopic data; the NOE experiments on Ha, Hb, Hc, and the aldehyde proton indicated that the aldehyde and all the ring-junction protons were cis. The formation of **4** provided further evidence that zirconacycle **2** was the intermediate and that it was formed regio- and stereoselectively. The mechanism for the formation of aldehyde **4** is unclear. However, we believe that the insertion of carbon monoxide into zirconacycle **2** produces **5**, which is then converted to π-allylzirconium complex **6**. Insertion of carbon monoxide into **6** and hydrolysis of the resultant zirconacycle with 10% HCl gives the saturated ketone **4**.

Treatment of diene **7** first with zirconocene and then with 10% HCl afforded perhydroindole **8** in high yield. Insertion of carbon monoxide into the zirconacycle prepared from **7** afforded tricyclic ketone **9** as a single isomer in 94% yield.

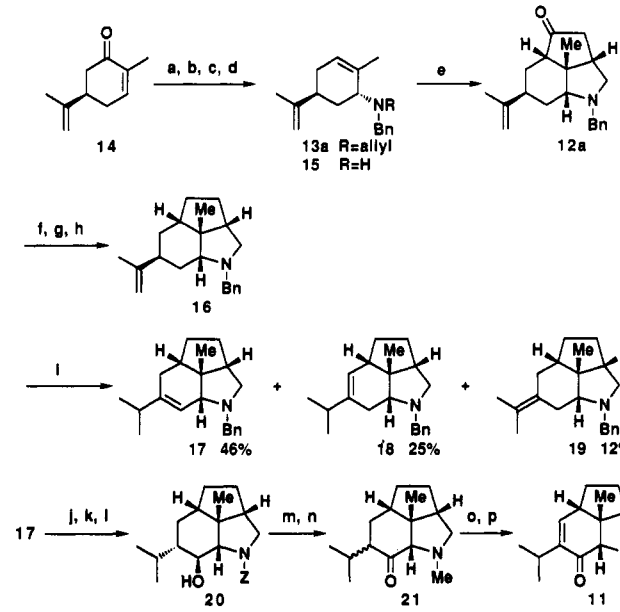
Because the skeleton of **9** is the same as that of the natural product dendrobine (**10**), we applied our one-pot, regio- and stereocontrolled preparation of tricyclic compounds to the synthesis of dendrobine.[5,6] Our retrosynthetic analysis is presented in Scheme III. Compound **12** should be obtained from the zirconium-promoted reductive cyclization of **13**. Compound **13** should be obtained from (−)-carvone (**14**), which is commercially available. Our question about this strategy was whether a compound having a substituent on the double bond would yield the desired product in the reductive cyclization.[7]

(−)-Carveol, prepared by the reduction of (−)-carvone with $NaBH_4$ in the presence of $CeCl_3$,[8] was treated with CBr_4 and PPh_3 in CH_2Cl_2 to give the cyclohexenyl bromide. The cyclohexenyl bromide was treated with CBr_4 and PPh_3 in CH_2Cl_2 to give the cyclohexenyl bromide. The cyclohexenyl bromide was treated with benzylamine[9] and then

Scheme III



Scheme IV[a]



[a] (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, rt, 12 h, 93%; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 15 min; (c) benzylamine, K_2CO_3, CH_3CN, rt, 12 h, 48% (two steps); (d) allyl bromide, K_2CO_3, CH_3CN, rt, 48 h, 78%; (e) (i) Cp_2ZrCl_2, BuLi, THF, rt, 3 h, (ii) CO, rt, 13 h, 47%; (f) $NaBH_4$, EtOH, rt, 12 h, 91%; (g) PhOCSCl, DMAP, CH_3CN, rt, 2 h; (h) Bu_3SnH, AIBN, toluene, 75 °C, 1.5 h, 67% (two steps); (i) TsOH, dichloroethane, reflux, 48 h; (j) $BH_3 \cdot THF$, diglyme, 0 °C, 30 min, then Me_3NO, reflux, 30 min, quant.; (k) H_2, 10% Pd–C, AcOH, rt, 3 h; (l) BnOCOCl, K_2CO_3, CH_2Cl_2, rt, 12 h, 83% (two steps); (m) $LiAlH_4$, Et_2O, 0 °C, 1 h, 92%; (n) Jones oxidation, rt, 6.5 h, 91%; (o) LDA, PhSeBr, HMPA, 0 °C, 1.5 h, 88%; (p) mCPBA, THF, −30 °C, 1 h, 73%.

(3) Mori, M.; Uesaka, N.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1222.

(4) Satisfactory elemental analyses or high-resolution mass spectra and spectroscopic data were obtained for all new compounds.

(5) Isolation of dendrobine: Suzuki, H.; Keimatsu, I.; Ito, K. *Yakugaku Zasshi* **1932**, *52*, 1049; *Ibid.* **1934**, *54*, 801.

(6) Total synthesis of dendrobine: (a) Kende, A. S.; Bentley, T. J., Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332. (b) Yamada, K.; Suzuki, M.; Hayakawa, Y.; Aoki, K.; Nakamura, H.; Nagase, H.; Hirata, Y. *Ibid.* **1972**, *94*, 8278. Inubushi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *Chem. Pharm. Bull.* **1974**, *22*, 349. Trost, B. M.; Tasker, A. S.; Rüther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670. Roush, W. R. *Ibid.* **1980**, *102*, 1390. Martin, S. F.; Li, W. *J. Org. Chem.* **1991**, *56*, 642.

(7) Zirconium-promoted reductive coupling of an enyne with a substituent on the double bond afforded a product resulting from intermolecular coupling of the alkynes. However, similar treatment of a nitrogen-containing compound afforded the desired cyclized product in good yield.[2c]

(8) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

with allyl bromide to give cyclohexenylamine **13a**. Cyclization of **13a** with zirconocene proceeded smoothly to give the zirconacycle, which was treated with carbon monoxide at room temperature to provide the desired tricyclic ketone **12a** in 47% yield.[10] The substituent on the double bond of **13a** did not affect the zirconium-promoted reductive cyclization. Next, we attempted to isomerize the double bond of **12a** into the six-membered ring using an organometallic complex such as $RhCl_3$, $RhCl(PPh_3)_3$, or 10% Pd–charcoal, but we were unsuccessful. We overcame this problem by converting the ketone of **12a** into a methylene with $NaBH_4$ and treating the resultant product first with PhOCSCl and then with Bu_3SnH in the presence of AIBN to give compound **16** in 61% yield (3 steps). Heating **16** in the presence of TsOH in dichloroethane smoothly isomerized the double bond and afforded isomers **17**, **18**, and **19** in 46%, 25%, and 12% yields, respectively. The thermodynamically most stable isomer was **17**. Because the isomers were in a state of equilibrium in the presence of acid, **18** and **19** could be converted into **17** by heating them with TsOH in dichloroethane. Hydroboration of **17** followed by oxidation with trimethylamine *N*-oxide provided the corresponding alcohol. The benzyl group was converted to a benzyloxycarbonyl group by hydrogenolysis with 10% Pd–charcoal and subsequent treatment with carbobenzyloxy chloride in the presence of K_2CO_3. $LiAlH_4$ reduction of the carbamate **20**, followed by Jones oxidation, afforded the desired ketone **21** as a mixture of epimers. Compound **21** was treated with LDA and PhSeBr, and subsequent MCPBA oxidation afforded **11**, Kende's intermediate.[6a] The structure of **11** was confirmed by spectroscopic data.

In conclusion, a one-pot stereoselective synthesis of perhydroindole derivatives and tricyclic ketones from easily obtainable starting materials was developed using zirconium-promoted reductive cyclization. The formal total synthesis of dendrobine was achieved from the tricyclic ketone **12a**, which was prepared from (−)-carvone by a short sequence of steps.

(9) Unfortunately, compound **15** (R = H) was not optically pure (15% ee). The determination of the enantiomeric purity of compound **15** will be reported in a future article. The study of the total synthesis of optically pure dendrobine is now in progress.

(10) Cyclization of compound **13** where R = Me was unsuccessful.

Enolate Reactions on Macrocyclic Ring Systems. Total Synthesis of (±)-Sarcophytol A†

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Summary: The stereoselective synthesis of (±)-sarcophytol A and a discussion of the stereoselectivity in the β-elimination of alkoxy group of the macrocyclic enolate based on MM2 calculations are presented.

Sarcophytol A, isolated from a soft coral, *Sarcophyton glaucum*, is a cembrane-type diterpene[1] which inhibits tumor promotion by teleocidin in two-stage carcinogenesis in mouse skin.[2] We report here an efficient synthesis of sarcophytol A (**1**) by "enone switching"[3] using the β-alkoxy-α-ethylidene macrocyclic ketone **2** (Figure 1). Macrocycles have the π-orbitals of olefins oriented in the plane of the ring to minimize transannular nonbonded repulsions.[4] Therefore, macrocyclic reactions should give different senses and degrees of diastereoselectivity from those in normal five- and six-membered rings and acyclic compounds. There are extensive studies on the stereocontrolled enolate reactions in the usual cyclic and acyclic structures.[5] However, it is quite difficult to predict the stereoselectivity of macrocyclic enolate reactions[4,6] because of their many conformational possibilities. It would be an important advance if this problem could be solved.

Molecular mechanics calculations and MM2 transition structure models[7] have proven useful for prediction (or analysis) of stereoselectivity in macrocyclic reactions.[4,8] We have achieved a stereoselective synthesis of sarcophytol A (**1**) (Scheme I) in which the crucial 14-membered dienone **7** is constructed by intramolecular alkylation[9] of the protected cyanohydrin **3**, prepared from vinyl bromide **9** and farnesyl acetate **10**. The *E,Z*-diene at C(4) and C(2) in **7** is introduced stereoselectively by 1,4-addition of lithium dimethylcuprate to enone **4** followed by β-elimination of the methoxymethoxy group.[10] As described below, MM2 calculations of the various possible conformations of the exocyclic enone **4** and its likely *Z*- and *E*-enolate intermediates **5** and **6** suggest that Michael ad-

† Dedicated to Professor Gilbert Stork on the occasion of his 70th birthday.

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(1) Isolation: (a) Kobayashi, M.; Nakagawa, T.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2382. Synthesis: (b) Takayanagi, H.; Kitano, Y.; Morinaka, Y. *Tetrahedron Lett.* **1990**, *31*, 3317.

(2) Fujiki, H.; Suganuma, M.; Suguri, H.; Yoshizawa, S.; Takagi, K.; Kobayashi, M. *J. Cancer Res. Clin. Oncol.* **1989**, *115*, 25.

(3) (a) Takahashi, T.; Hori, K.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 119. (b) Takahashi, T.; Hori, K.; Tsuji, J. *Chem. Lett.* **1981**, 1189. (c) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590.

(4) (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275.

(5) (a) House, H. O.; Phillips, W. V.; VanDerveer, D. *J. Org. Chem.* **1979**, *44*, 2400. (b) Zimmerman, H. E.; Linder, L. W. *J. Org. Chem.* **1985**, *50*, 1637. (c) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Yamamoto, K. *Tetrahedron Lett.* **1989**, *30*, 4999. (d) Yamada, H.; Shimizu, K.; Nisar, M.; Takahashi, T.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 2407.

(6) Takahashi, T.; Yamashita, Y.; Doi, T.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 4273.

(7) (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (b) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499. (c) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J.; Fukazawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 2674.

(8) (a) Abelmann, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. (b) Marshall, J. A.; Jensen, T. M.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 4316. (c) Takahashi, T. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier Science: B. V.: Amsterdam, 1991; Vol. 8, pp 175.

(9) (a) Stork, G.; Depezay, J. C.; d'Angelo, J. *Tetrahedron Lett.* **1975**, 389. (b) Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005.

(10) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

0022-3263/92/1957-3521$03.00/0