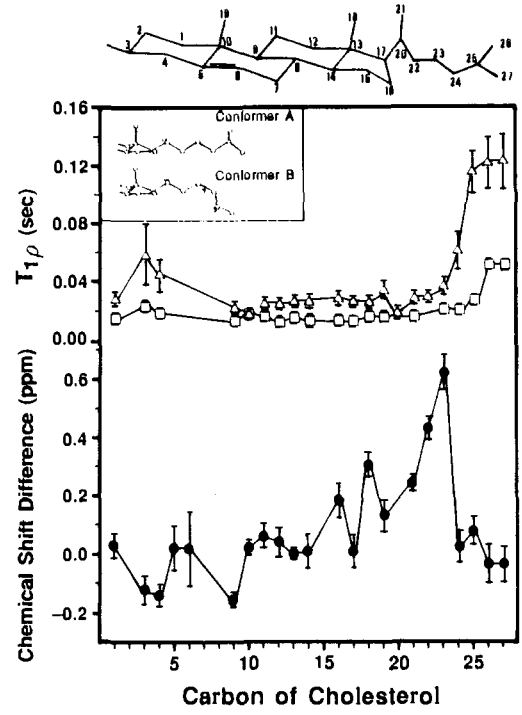

Figure 2. ^{13}C NMR chemical shift differences and $T_{1\rho}$ (^1H) of LPC(10:0)/cholesterol and LPC(20:0)/cholesterol mixtures as a function of the carbon positions of the cholesterol molecule. Over 10 different contact times in the interval between 0.1 and 32 ms were used for the determination of $T_{1\rho}$. The error bars of the $T_{1\rho}$ values represent the standard deviation obtained from the least-squares fitting of the intensities of spectra as a function of contact time.[6] The open triangle and square symbols represent $T_{1\rho}$ obtained fromLPC(10:0)/cholesterol and LPC(20:0)/cholesterol mixtures, respectively. A schematic diagram of the cholesterol molecule is shown at the top of the figure to indicate that only those signals from the terminal isooctyl side chain showed marked variation in the demonstrated NMR parameters. Two conformations of the cholesterol side chain derived from crystal structures[14] are also included in the figure to explain the results. The arrow shown in conformer B refers to the ω_4 (C_{22}–C_{23}–C_{24}–C_{25}) gauche torsion angle. A model based on the trans-to-gauche isomerization at ω_4 can explain the elevated $T_{1\rho}$ values of the terminal ^{13}C signals from C_{24} to C_{27} and the upfield displacement of the chemical shift of the C_{22} and C_{23} signals for the cholesterol side chain of the LPC(10:0)/cholesterol mixture.

was detected at C_{23}; the $T_{1\rho}$ values of C_{23} signals were similar to those of cholesterol condensed ring signals. Since differences in the chemical shift and $T_{1\rho}$ of the ^{13}C NMR spectrum reflect changes in the conformation and dynamics of the molecule,[8] some motional and conformational changes must be introduced along the C_{23}–C_{24} bond of the cholesterol side chain in the LPC(10:0)–cholesterol complex.

On the basis of the ^2H NMR studies on the 7/3 molar ratio of dimyristoylphosphatidylcholine/cholesterol bilayer at 25 °C, the cholesterol side chain was found to be as rigid as the condensed four-ring structure up to C_{22}.[13] The labeled deuterons at C_{24} were also highly ordered with probably an extended trans conformation at ω_4. On the other hand, the 123 crystallographically independent determinations of the cholestane side chain show that the chain has four principal conformations,[14] of which the A and B conformers (Figure 2) are trans and gauche, respectively, for the ω_4 torsion angle. By adopting the ±gauche form at the ω_4 torsion angle, C_{22} and C_{23} are brought to juxtaposition with the terminal carbon atoms. The observed upfield displacement of the chemical shifts of C_{22} and C_{23} signals can then be understood as the γ-gauche effect.[15] Taking all the available data together, we suggest that the ω_4 torsion angle is trans for the cholesterol side chain of the LPC(20:0)/cholesterol mixture, whereas it undergoes trans-to-gauche isomerization for that of the LPC(10:0)/cholesterol mixture. The hydrocarbon chain length of the LPC(10:0) molecule is approximately 6 Å shorter than that of the cholesterol molecule. The cholesterol side chain may be forced to adopt a *less* extended conformation to minimize the void volume created by the LPC(10:0)–cholesterol complex in the lamellar structure.

(13) Dufourc, E. J.; Parish, E. J.; Chitrakorn, S.; Smith, I. C. P. *Biochemistry* **1984**, *23*, 6062–6071.
(14) Duax, W. L.; Wawrzak, Z.; Griffin, J. F.; Cheer, C. In *Biology of Cholesterol*; Yeagle, Ed.; CRC Press: Boca Raton, FL, 1988; Chapter 1.
(15) Saito, H. *Magn. Reson. Chem.* **1986**, *24*, 835–852.

Synthesis of 3,4-Disubstituted Indoles via a Sequential Olefin-Insertion/Ene Route†

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Substituted indoles are structural components of a vast number of important natural products;[1] thus they represent attractive synthetic targets.[2] Historically, two approaches have been most often used for the synthesis of 3,4-disubstituted indoles. The first constructs the indole nucleus using an annelation strategy, employing a polysubstituted aromatic precursor. Included in this category are the Fischer,[3] Madelung,[4] Reissert,[5] and Batcho–Leimgruber[6] indole syntheses. In the second approach, the 3- and 4-positions of a preformed indole nucleus are selectively functionalized. Often these methods produce a mixture of regioisomers.[7] In this paper we report a fundamentally different route to these important molecules. Of particular significance is the complete regioselectivity of the method and its utilization of readily available starting materials.

During the past few years we have developed a general means for the generation of zirconocene complexes of substituted benzynes.[8] These species can serve as useful vehicles for the preparation of a variety of polysubstituted aromatic molecules via their

†This paper is dedicated to our friend and colleague Professor George Büchi, in recognition of his many notable contributions to the field of indole chemistry.

(1) (a) *The Alkaloids*; The Chemical Society: London, 1971; Specialist Periodical Reports. (b) Saxton, J. E. *Nat. Prod. Rep.* **1989**, *6*, 1. (c) Hesse, M. *Alkaloid Chemistry*; Wiley: New York, 1978. (d) Cordell, G. A. *Introduction to Alkaloids: A Biogenetic Approach*; Wiley: New York, 1981. (e) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman: London, 1981. (f) Pindur, A. R. *J. Heterocycl. Chem.* **1988**, *25*, 1.

(2) (a) Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267. (b) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (c) Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1988**, *44*, 7325. (d) Somei, M.; Yamada, F.; Naka, K. *Chem. Pharm. Bull.* **1987**, *35*, 1322. (e) Somei, M.; Yamada, F.; Hamada, H.; Kawasaki, T. *Heterocycles* **1989**, *29*, 643. (f) Masuda, T.; Ueda, K.; Asano, O.; Nakatsuka, S. *Heterocycles* **1987**, *26*, 1475. (g) Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783. (h) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170. (i) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106. (j) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harringron, P. J. *J. Org. Chem.* **1989**, *54*, 4141. (k) Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 683.

(3) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

(4) Brown, R. K. *Indoles*; Wiley-Interscience: New York, 1972. (b) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.

(5) Lloyd, D. H.; Nichols, D. E. *Tetrahedron Lett.* **1983**, *24*, 4561. (b) Haefliger, W.; Knecht, H. *Tetrahedron Lett.* **1984**, *25*, 285.

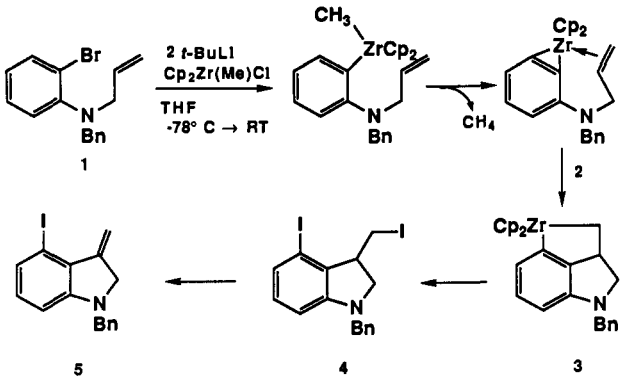
(6) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.

(7) For instance, see: (a) Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1988**, *44*, 7325. (b) Widdowson, D. A. *Pure Appl. Chem.* **1990**, *62*, 575. (c) Somei, M.; Yamada, F.; Naka, K. *Chem. Pharm. Bull.* **1987**, *35*, 1322. (d) Somei, M.; Yamada, F.; Hamada, H.; Kawasaki, T. *Heterocycles* **1989**, *29*, 643. (e) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623.

(8) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1044.

0002-7863/91/1513-4685$02.50/0

Scheme I



insertion reactions with unsaturated organic compounds which proceed with nearly complete regiocontrol.[9] The majority of our work has dealt with intermolecular reactions, but we reasoned that the intramolecular reaction[10] of an *N*-allylaniline, in which a zirconocene complex of benzyne was suitably disposed, could lead to a 3,4-difunctionalized indoline derivative, and we report here our results.

Treatment of a mixture of *N*-allyl-*N*-benzyl-2-bromoaniline (Scheme I) and zirconocene (methyl) chloride with 2 equiv of *tert*-butyllithium in THF at −78 °C, followed by warming to room temperature, produced tricyclic zirconacycle **3**. Metallacycle **3** is presumably formed through the intermediacy of benzyne complex **2**, via insertion of the pendant olefin. It should be noted that in this process the indoline nucleus is formed from a monocyclic precursor, and the 3- and 4-positions are necessarily functionalized with total regiochemical control. Treatment of **3**, which is usually accomplished without its isolation, with an excess of I_2 in CH_2Cl_2 leads to diiodide **4** in 70% overall yield from **1**. If **4** is heated in the presence of DBU at 65 °C in toluene, dehydrohalogenation takes place in nearly quantitative yield to give **5**. Under these conditions, little or no isomerization to the corresponding skatole derivative is observed.[11] While **5** has been characterized spectroscopically,[12] its instability has precluded its isolation in pure form.

The relationship of **5** to its aromatic isomer prompted us to study its participation in ene reactions.[13] The ene process could be induced under particularly mild conditions (85 °C, toluene, 2–12 h) by treatment of **5** with a variety of active enophiles to produce 4-iodoindole derivatives **6** (Scheme II). An initial investigation of the scope of this reaction was undertaken with the results shown in Table I. For example, heating a toluene solution of **5** in the presence of diethyl acetylenedicarboxylate (2.1 equiv) gave diester (entry 1) in 53% yield as a single isomer after workup and chromatographic purification. Similarly, activated carbonyls provide α-hydroxymalonate (entry 4) and -propionate (entry 5)

Scheme II

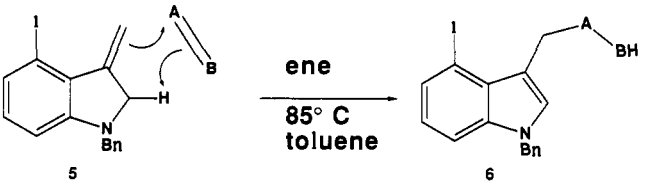
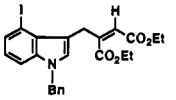
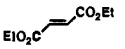
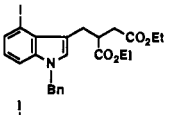
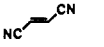
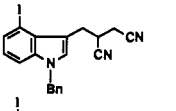
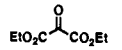
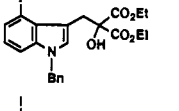
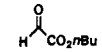
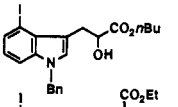
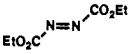
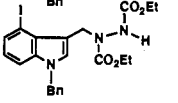
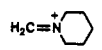
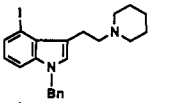
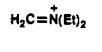
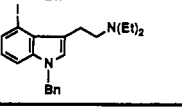


Table I

Entry	Ene Substrate	Product	Yield[a] (%)
1	$EtO_2C{-}{\equiv}{-}CO_2Et$		53
2			56
3			60
4			76
5			72
6			83
7			70
8			85

[a] Yields refer to isolated yields of purified products based on diiodide precursor.

derivatives in good yield. In addition, nitrogen-containing enophiles proved to be especially good substrates; in entries 7 and 8, 4-iodotryptamine analogues were produced in good to excellent yields upon treatment of **5** with the corresponding iminium ions.[14]

These experiments establish a fundamentally new approach for the construction of highly substituted indole derivatives. The scope of this and related transformations and their application to the synthesis of natural products is under investigation.

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Supplementary Material Available: Experimental details for the preparation and spectroscopic characterization of **1–6** (9 pages). Ordering information is given on any current masthead page.

(9) (a) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137. (b) Buchwald, S. L.; Fang, Q. *J. Org. Chem.* **1989**, *54*, 2793.

(10) For lead references on intramolecular reactions using low valent zirconium reagents, see: (a) Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. (b) 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. (c) Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1989**, *111*, 4495.

(11) For related compounds, see: (a) Boger, D. L.; Ishizaki, T.; Kitos, P. A.; Suntonwat, O. *J. Org. Chem.* **1990**, *55*, 5823. (b) Boger, D. L.; Colemen, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796. (c) Dittami, J. P.; Ramanathan, H. *Tetrahedron Lett.* **1988**, *29*, 45. (d) Tanaka, H.; Murakami, Y.; Okamoto, K.; Aizawa, T.; Torii, S. *Bull. Chem. Soc.* **1988**, *61*, 310. (e) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282. (f) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 1133.

(12) ^1H NMR (C_6D_6): δ 3.67 (t, 2 H, J = 3.00 Hz), 3.77 (s, 2 H), 4.66 (t, 1 H, J = 2.75 Hz), 6.14 (d, 1 H, J = 7.93 Hz), 6.42 (t, 1 H, J = 7.93 Hz), 6.52 (t, 1 H, J = 3.06 Hz), 6.9–7.2 (m, 6 H).

(13) For reviews of the ene reaction, see: (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (c) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (d) Taber, D. F. *Intramolecular Diels–Alder and Alder–Ene Reactions*; Springer-Verlag: Berlin, 1984.

(14) (a) Rochin, C.; Babot, O.; Dunogues, J.; Duboudin, F. *Synthesis* **1986**, 228. (b) Stewart, T. D.; Bradley, W. E. *J. Am. Chem. Soc.* **1932**, *54*, 4173.