Titanocene-Based Method for Indole Synthesis

Kazumasa Aoki, Andrew J. Peat, and Stephen L. Buchwald*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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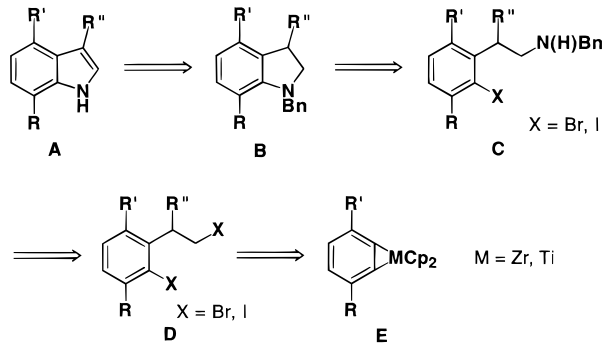
Abstract: A new approach for the construction of indoles employing the air- and moisture-stable reagent Cp_2TiCl_2 is described. The key steps involved are (1) the intermolecular insertion reactions of an olefin and a titanocene-stabilized benzyne complex and (2) the Pd-catalyzed aryl amination reaction. The simplicity and availability of the requisite starting materials give the method a broad scope for the preparation of polysubstituted indoles.

Introduction

The synthesis of functionalized indoles has been of interest to organic chemists for many years due to the large number of natural products that contain this structural element.[1] More importantly, indole-containing compounds have pronounced effects in many physiological processes.[2] For these reasons, numerous methods exist to construct the indole skeleton.[3] Recently, we reported a synthesis of substituted indolines which involves the intramolecular olefin insertion reactions of a zirconocene-stabilized benzyne complex.[4] This allows for the one-pot synthesis of regiochemically pure 3,4-diiodoindolines, which served as convenient precursors to the analogous indole derivatives including intermediates in the total or formal syntheses of several natural products, such as makaluvamine C, damirones A and B, dehydrobufotenine, the pharmacophore of CC-1065, and the clavicipitic acids.[5] Although the method is regioselective and is compatible with a variety of functional groups, we recognized the major drawback to its use was the need to employ the air- and moisture-sensitive complex $Cp_2Zr(Me)Cl$. In addition, the synthesis of the other starting material, an *N*-allyl-*o*-bromoaniline, can be difficult, depending upon the nature of the substitution of the aromatic ring. Additionally, the method is limited to the formation of indoles bearing substituents at both the 3- and 4-positions. In an effort to ameliorate these problems, we decided to investigate an alternative route. Herein, we describe a novel approach for the synthesis of indoles involving the intermolecular insertion reaction of an olefin with a titanocene-benzyne complex. The required starting materials, an aryl Grignard reagent, an olefin, a primary amine, and the air-stable reagent, Cp_2TiCl_2, are commercially available or readily prepared. This imparts this method with a wide generality for the synthesis of polysubstituted indoles.

Scheme 1



Results and Discussion

The retrosynthetic analysis for our indole synthesis is shown in Scheme 1. The indole system **A** is constructed from the indoline adduct **B**, which is formed from 2-bromophenethylamine **C** via a palladium-catalyzed ring closure of the five-membered ring.[6] The amine **C** is formed from dibromide **D**, which in turn is prepared from the appropriate metallocene−benzyne complex **E**.[7]

Research from our laboratories provides a means for the ready access to the requisite dihalide **D** via intermolecular insertion

(1) (a) *The Alkaloids*; Specialist Periodical Reports; The Chemical Society: London, 1971. (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) Hugel, H. M.; Kennaway, D. *J. Org. Prep. Proc. Int.* **1995**, *27*, 1. (b) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.

(3) (a) Sundberg, R. J. *Indoles;* Academic Press: San Diego, CA, 1996 and refernces therein. (b) Gribble, G. W. *Contemp. Org. Synth.* **1994**, *1*, 145. (c) Robinson, B. *The Fischer Indole Sythesis*; Wiley-Interscience: New York, 1982. (d) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

(4) Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685.

(5) (a) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028. (b) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797 and references therein. (c) Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164. (d) Tidwell, J. H.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 6380. (e) see also Tietze, L. F.; Buhr, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1366.

(6) For recent examples of this methodology, see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (e) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348. (f) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (g) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(7) (a) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137. For recent reviews of Zr−benzyne chemistry, see: (b) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696. (c) Buchwald, S. L.; Broene, R. D. In *Comprehensive Organometallic Chemistry*, 2nd ed.; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press, Oxford, U.K., 1995; Vol. 12, Chapter 7.4, pp 771−784.

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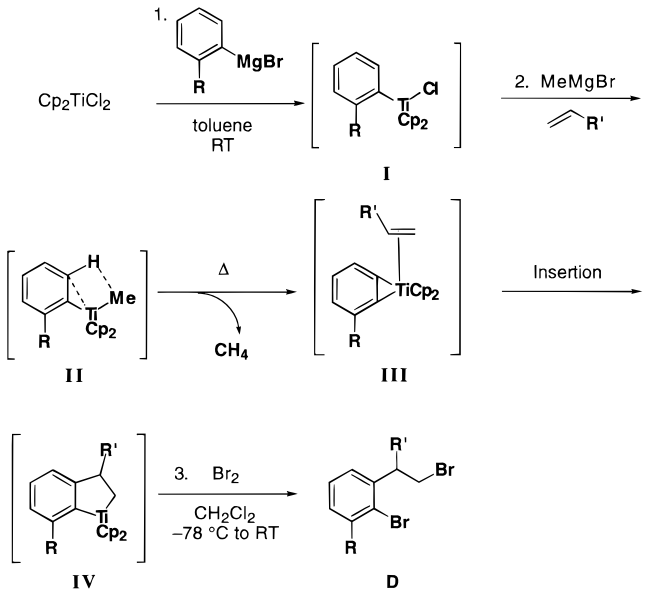
Scheme 2



of an olefin into the Zr−C bond of a zirconocene−benzyne complex, followed by treatment of the intermediate zirconacycle with iodine.[7] In our previous method, **E** (M = Zr) was generated by the addition of an aryllithium reagent to Cp_2Zr(Me)Cl. In an effort to simplify the experimental procedure for the preparation of **E**, we modified the previous method by using titanocene dichloride in lieu of zirconocene methyl chloride. This substitution has two advantages: (1) titanocene dichloride is air- and moisture-stable and (2) the titanium complex should exhibit greater functional group tolerance than the corresponding highly oxophilic, zirconium reagent.[8] Treatment of titanocene dichloride with an *o*-substituted aryl Grignard reagent (1.1 equiv) in toluene at 25 °C cleanly affords arylchlorotitanocene **I** (Scheme 2). It should be noted that the analogous aryllithium reagents do not give **I**, but instead reduce the metal complex to a Ti(III) species.[9] An olefin (2.0 equiv) and MeMgBr (1.0 equiv) are added to the reaction mixture to produce arylmethyltitanocene **II**, which upon heating generates the titanocene-stabilized benzyne complex **III**. The olefin coordinates to the metal opposite from the *o*-aryl substituent,[7] with the olefin R′-substituent situated away from the cyclopentadienyl ligands as depicted in intermediate **III**.[7] Insertion of the olefin into the carbon−titanium bond of the benzyne complex yields metallacyclopentane **IV**.[10] The toluene was removed in vacuo, CH_2Cl_2 was added, and the solution was cooled to −78 °C. Addition at −78 °C of a solution of bromine in CH_2Cl_2 produces the desired dibromide **D** in moderate yield with excellent regiochemical purity. The overall process increases the level of substitution of the aromatic ring by one, thereby producing a contiguously trisubstituted benzene derivative. It should be noted that the formation of the dibromide is the yield-limiting step in all of the following procedures.

With a method to prepare dibromides **D** in hand, we turned our attention to their conversion to indolines. Our original idea was to convert **D** to the corresponding amine **C**, and then close the five-membered ring via the Pd-catalyzed intramolecular aryl amination reaction.[6] After much experimentation, we found that

Scheme 3

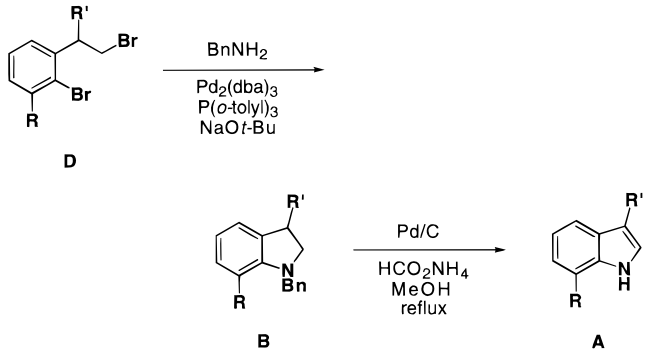
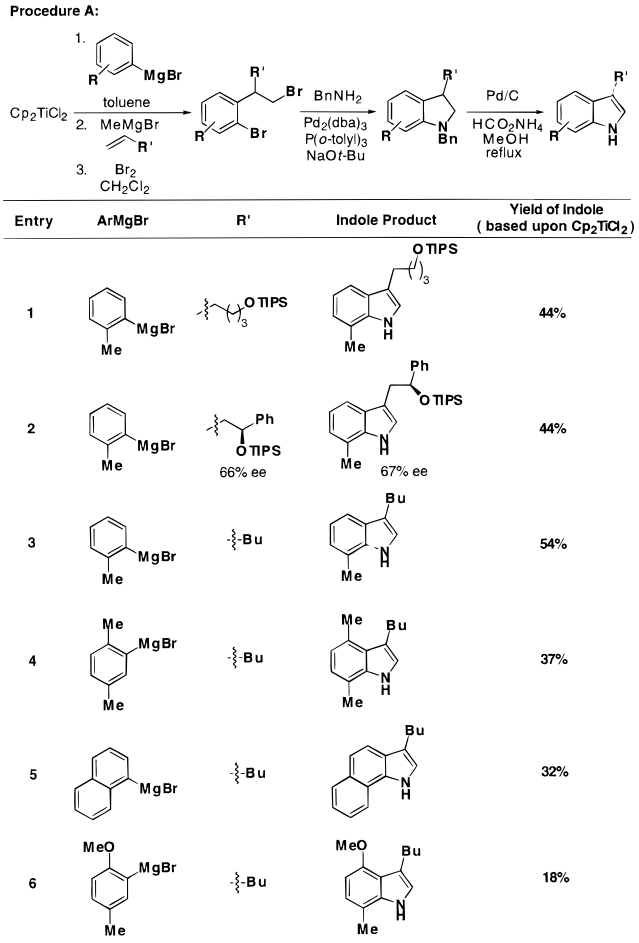


Table 1



it was not necessary to isolate the amine. Instead, the dibromide could be converted directly to the indoline derivative (Scheme 3). Treatment of **D** with benzylamine, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and NaO-*t*-Bu in toluene affords the indoline **B** in good overall yield. At this stage it was necessary to remove the P(*o*-tolyl)$_3$ by flash chromatography since it hinders the subsequent reaction. Deprotection and oxidation of indoline **B** with Pd/C and ammonium formate gives the desired indole **A**.[11]

A variety of substituted indoles were prepared using this three-step procedure (Table 1). Initially, we used the commercially available *o*-tolylmagnesium bromide to test the feasibility of our approach. Insertion of olefins containing TIPS-protected alcohols (entries 1 and 2) gave good overall yields of

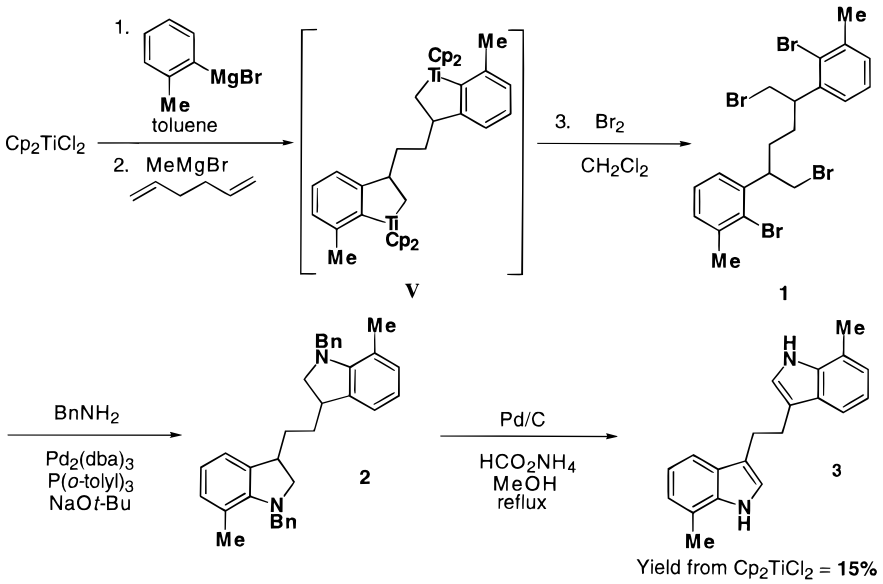
(8) Cardin, D. J.; Lappert, M. F.; Raston, C. L. *Chemistry of Organo-zirconium and -hafnium Compounds*; Wiley: New York, 1986.

(9) (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703. (b) Martin, H. A.; Jellinek, F. *J. Organomet. Chem.* **1968**, *12*, 149.

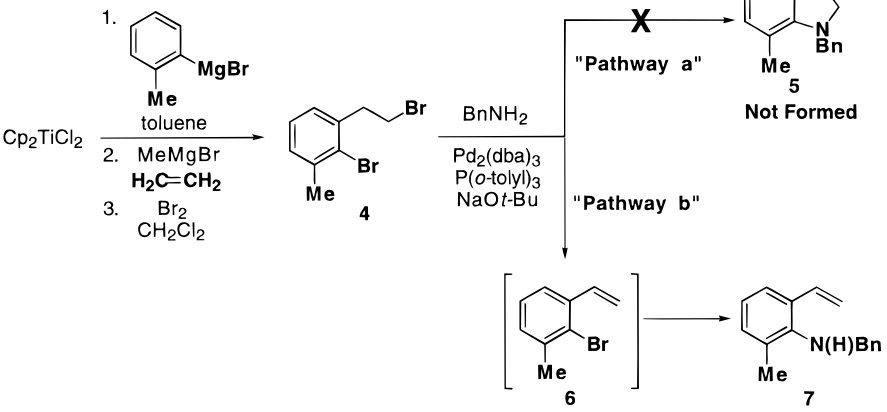
(10) Cámpora, J.; Buchwald, S. L. *Organometallics* **1993**, *12*, 4182.

(11) Kiguchi, T.; Kuninobu, N.; Takahashi, Y.; Yoshida, Y.; Naito, T.; Ninmiya, I. *Synthesis* **1989**, 778.

Scheme 4



Scheme 5



the indole derivatives. It should be noted that no racemization was detected when an enantiomerically enriched TIPS-protected alcohol[12] was used (entry 2). Also, 1-hexene was inserted to give 3-butyl-7-methylindole in 54% yield (entry 3). In addition to *o*-tolylmagnesium bromide, the use of disubstituted aryl Grignard reagents allowed for the construction of trisubstituted indole derivatives (entries 4−6). For example, 1-naphthylmagnesium bromide and 1-hexene produced the 3-butyl-naphthylindole in 34% yield.

The use of 1,5-hexadiene produced the interesting bis-indole **3** (Scheme 4). Addition of *o*-tolylmagnesium bromide, MeMgBr, and 1,5-hexadiene to a solution of titanocene dichloride in toluene afforded the bis-metallacyclopentane **V**, which was treated with bromine to form **1** as a mixture of diastereomers. The Pd-catalyzed aryl amination reaction proceeded smoothly using excess benzylamine to produce the bis-indoline adduct **2**. Finally, the benzyl groups were cleaved and the indoline rings were oxidized to afford bis-indole **3** in 15% overall yield from Cp_2TiCl_2.

In an effort to make the procedure as general as possible, we wished to determine whether we could synthesize indoles that were not functionalized at the 3-position. Such compounds are important precursors in the syntheses of more elaborate indole compounds.[1] With this in mind, we investigated the use of ethylene as the olefin component in our method (Scheme 5). A solution of titanocene dichloride in toluene in a Fischer−Porter bottle was treated with *o*-tolylmagnesium bromide at room temperature (RT) to generate the arylchlorotitanocene. The solution was cooled to 0 °C, and MeMgBr was added. After the mixture was stirred for 0.5 h, the Fischer−Porter bottle was charged with 30 psig of high-purity ethylene[13] and the vessel was heated to 65 °C for 16 h. The solution was cooled to 25 °C, the pressure was carefully vented, and the solvent was removed. Methylene chloride was added, the reaction vessel was cooled to −78 °C, and a solution of bromine in CH_2Cl_2 was added at this temperature. It should be noted that the success of the reaction is highly dependent upon the purity of the ethylene.[14] The conversion of the dibromide to the indoline system via the previously described protocol gave only trace amounts of the desired indoline adduct **5**. Instead, the major product was the styrene derivative **7**; formation of the indoline compound (pathway a) is slow compared to dehydrohalogena-

(12) Roush, W. R.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.

(13) The ethylene used was of Grade 5 quality (99.99% pure) and was purchased from Middlesex Gases & Technology Inc.

(14) We obtained only trace amounts of the desired product when using the 95% ethylene purchased from Aldrich Chemical Co.

(15) (a) *Prudent Practices in the Laboratory*; National Academy Press: Washington, DC, 1995. (b) Mohring, J. R.; Hammond, J. R.; Morrill, T. C.; Neckers, D. C. *Experimental Organic Chemistry*; Freeman: New York, 1998.

(16) Commercially available from Aldrich Chemical Co.

Scheme 6

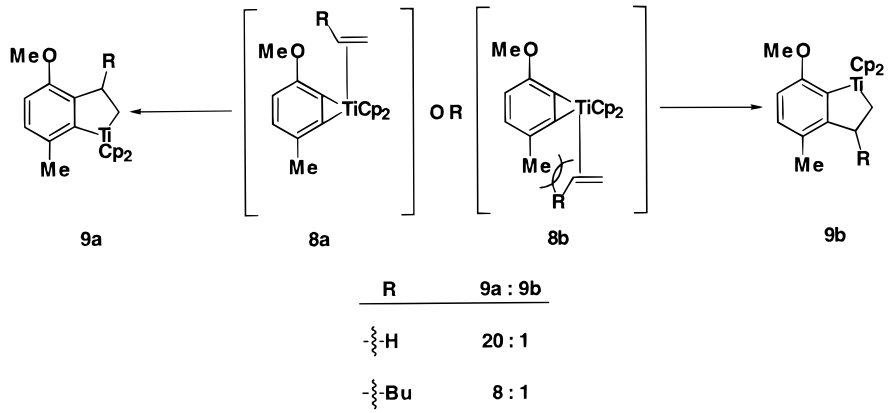
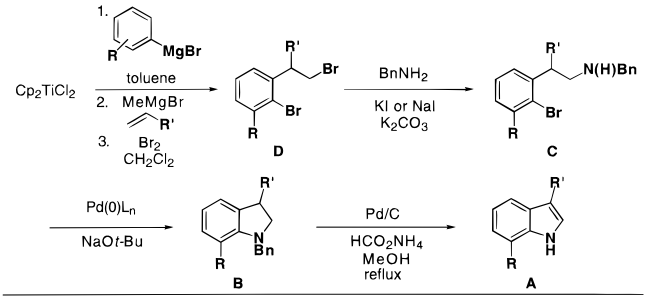
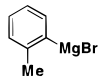
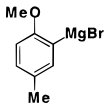
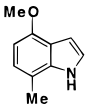
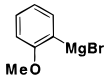
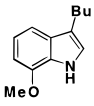
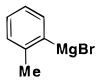
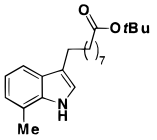


Table 2

Procedure B, C:



Entry	ArMgBr	R'	Indole Product	Yield of Indole (based upon Cp_2TiCl_2)
1		-H		41%
2		-H		30%
3		-Bu		38%
4				33%

tion (pathway b). We believe that elimination of HBr induced by NaO-*t*-Bu produces 2-bromo-3-methylstyrene (**6**), which then undergoes a cross-coupling reaction with benzylamine to give the aniline **7**. We reasoned that dehydrohalogenation could be circumvented by using an alternative protocol. This involved first displacing the alkyl bromide with benzylamine and isolating intermediate **C** (Table 2, Procedures B and C), followed by Pd-catalyzed formation of the five-membered ring. Treatment of dibromide **D** with excess benzylamine, NaI, and K_2CO_3 gave the desired amine **C** with little formation of the styrene byproduct. Closure of the five-membered ring by way of Pd catalysis proceeded smoothly to form indoline **B**. Indole **A** was formed using the procedure which employed 10 mol % Pd/C as described above. In addition to the dibromides derived from ethylene, several others gave only minor amounts of the desired indole products when the first procedure was used. However, we obtained much better yields of these compounds by switching to procedures B and C (entries 3 and 4). When an ester-containing olefinic substrate was examined, a ca. 4:1 ratio of the metallacycle to the product in which insertion of the carbonyl group into the Ti−C bond took place. Instead of using the bulky *tert*-butyl ester, for the analogous substrate containing a methyl ester, carbonyl insertion was the predominant course of the reaction.

The use of 2-methoxy-5-tolylmagnesium bromide gave access to 4,7-differentially disubstituted indole derivatives (Table 1, entry 6; Table 2, entry 2). Insertion of the olefin into the Ti−C bond of the unsymmetrical benzyne complex **8a,b** proceeded with a high degree of regioselectivity, especially when ethylene was used (Scheme 6). We believe that this selectivity is a result of the difference in size between the two substituents (Me versus OMe).[7] The olefin preferentially coordinates to the metal opposite from the larger methyl substituent, thereby favoring the formation of metallacycle **9a**. Treatment of metallacycles **9a**,**b** with bromine produces the two isomeric dihalide derivatives. We found that it was not necessary to separate these compounds. Instead, the crude mixture was used in the subsequent reactions and the major indole isomer, obtained in the final step of the reaction sequence, was easily purified by flash chromatography.

In summary, a novel procedure for the regioselective synthesis of substituted indoles has been developed. The key steps in this method are (1) the intermolecular reaction of an olefin with a titanocene-stabilized benzyne complex and (2) the Pd-catalyzed amination of an aryl bromide. We believe that this approach will allow for the facile construction of a variety of highly substituted indoles since the required starting materials are widely available. In addition, the use of titanocene dichloride removes the need to prepare air- and moisture-sensitive organometallic intermediates necessitated in our previous procedures. Further investigations on this and related methodologies are currently underway in our laboratories.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmospheres Co. drybox. Other reactions were performed under an atmosphere of argon or nitrogen. NMR spectra were recorded on a Varian XL-300 or VXR-500 or a Bruker AC250 FT spectrometer. IR spectra were recorded on a Perkin-Elmer Series 1600 FT spectrometer. Gas chromatography analyses were performed on a Hewlett-Packard model 5890 GC with a 3392A integrator and FID detector using a 25-m capillary column with cross-linked SE-30 as a stationary phase. Electron impact mass spectra and high-resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, diethyl

ether, and hexane were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2 under nitrogen followed by distillation. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Aldrich Chemical Co. and was used without further purification. Cp_2TiCl_2 was a gift from Boulder Scientific Inc. (Mead, CO). All other reagents either were prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on E. M. Science Kieselgel 60 (230−400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ^{1}H NMR and either capillary GC or combustion analysis. All reported yields are representative. Elemental analyses were performed by E & R Microanalytical Laboratory, Inc. (Corona, NY).

General Procedure A. A solution of arylmagnesium bromide (1.1 equiv) in THF was added dropwise to a solution of Cp_2TiCl_2 (1.0 equiv, typically 2−4 mmol) in toluene (∼0.08 M) at RT under argon in a resealable Schlenk flask. After 1 h, the olefin (2.0 equiv) and a solution of MeMgBr (1.0 equiv) in Et_2O was added, then the flask was sealed and heated to 50 °C for 4 h. The solution was cooled to RT, and the solvent was removed in vacuo. Upon the addition of CH_2Cl_2 (12 mL/mmol of Cp_2TiCl_2), the solution was cooled to −78 °C and a solution of Br_2 (2.05 equiv) in CH_2Cl_2 (6 mL/mmol of Cp_2TiCl_2) at −78 °C was added dropwise. The solution was warmed slowly to RT, then the solvent was removed in vacuo. *Caution*: care should be used to ensure that excess bromine has been destroyed. Hexane (30 mL/mmol of Cp_2TiCl_2) was added, then the mixture was filtered through Celite, and the solvent was removed using a rotary evaporator. The dibromide product was partially purified by flash chromatography, and a portion of the material (typically ca. 25−50%) was used directly in the next step.

The dibromide (1.0 equiv) was treated with $Pd_2(dba)_3$ (4 mol %), P(*o*-tolyl)$_3$ (16 mol %), NaO-*t*-Bu (4.0 equiv), and benzylamine (2.0 equiv) in toluene. The flask was sealed then heated to 80 °C for 16 h. Upon cooling to RT, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed using a rotary evaporator. The indoline product was partially purified by flash chromatography, and a portion of the material (typically ca. 50%) was used directly in the next step.

The indoline derivative (1.0 equiv) was treated with 10 mol % (by weight) Pd/C (10 mol %) and ammonium formate (10.0 equiv) in MeOH. The solution was heated to reflux for 1.5 h, then allowed to cool to RT and filtered through Celite. The solvent was removed using a rotary evaporator, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography.

General Procedure B. A solution of arylmagnesium bromide (1.1 equiv) in THF was added dropwise to a solution of Cp_2TiCl_2 (1.0 mmol) in toluene at RT under argon in a Fischer−Porter bottle. After 1 h, the solution was cooled to 0 °C and a solution of MeMgBr (1.0 equiv) was added dropwise. After 0.5 h, the bottle was charged with 30 psig of ethylene and the solution was heated to 50 °C for 8 h. *Caution:* reactions at elevated pressure should be run behind a safety shield. The solution was cooled to RT, the pressure was carefully vented, and the solvent was removed in vacuo. Upon the addition of CH_2Cl_2 (6 mL/mmol of Cp_2TiCl_2), the solution was cooled to −78 °C. At this point, a solution of Br_2 (2.05 equiv) in CH_2Cl_2 (12 mL/mmol of Cp_2TiCl_2) at −78 °C was added dropwise. The solution was warmed slowly to RT, then the solvent was removed in vacuo. *Caution:* care should be used to ensure that excess bromine has been destroyed. Hexane (30 mL/mmol of Cp_2TiCl_2) was added, then the mixture was filtered through Celite, and the solvent was removed using a rotary evaporator. The dibromide product was partially purified by flash chromatography and used directly in the next step.

The dibromide (1.0 equiv) was treated with benzylamine (6.0 equiv), K_2CO_3 (6.0 equiv), and NaI (6.0 equiv) in THF, then the mixture was heated to 65 °C for 12 h. Upon cooling to RT, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and filtered, and the solvent was removed using a rotary evaporator. The excess benzylamine was removed by Kugelrohr distillation. The desired product was partially purified by flash chromatography and used directly in the next step.

A mixture of $Pd_2(dba)_3$ (2 mol %), P(*o*-tolyl)$_3$ (8 mol %), and NaO-*t*-Bu (1.4 equiv) was added to a solution of the amine (1.0 equiv) in toluene, and the flask was heated to 80 °C for 16 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_2O and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo. The indoline product was partially purified by flash chromatography and used directly in the next step.

The indoline derivative (1.0 equiv) was treated with 10 mol % (by weight) Pd/C (10 mol %) and ammonium formate (10.0 equiv) in MeOH. After heating to reflux for 24 h, the solution was cooled to RT and filtered through Celite. The solvent was removed using a rotary evaporator, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography.

General Procedure C. A solution of arylmagnesium bromide (1.1 equiv) in THF was added dropwise to a solution of Cp_2TiCl_2 (1.0 equiv, typically 4 mmol) in toluene (∼0.08 M) at RT under argon in a resealable Schlenk flask. After 1 h, the olefin (2.0 equiv) and a solution of MeMgBr (1.0 equiv) in Et_2O was added, then the flask was sealed and heated to 50 °C for 4 h. The solution was cooled to RT, and the solvent was removed in vacuo. To the flask was added CH_2Cl_2 (12 mL/mmol of Cp_2TiCl_2), and the solution was cooled to −78 °C. At this point a solution of Br_2 (2.05 equiv) in CH_2Cl_2 (6 mL/mmol of Cp_2TiCl_2) at −78 °C was added dropwise. The solution was warmed slowly to RT, then the solvent was removed in vacuo. *Caution*: care should be used to ensure that excess bromine has been destroyed.[15] Hexane (30 mL/mmol of Cp_2TiCl_2) was added, then the mixture was filtered through Celite, and the solvent was removed using a rotary evaporator. The dibromide product was partially purified by flash chromatography, and a portion of the material (typically ca. 30%) was used directly in the next step.

The dibromide (1.0 equiv) was treated with benzylamine (4.0 equiv), K_2CO_3 (4.0 equiv), and KI (2.0 equiv) in DMF, then the mixture was heated to 100 °C for 4 h. After cooling to RT, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and filtered, and the solvent was removed using a rotary evaporator. The amine product was partially purified by flash chromatography, and a portion of the material (typically ca. 75%) was used directly in the next step.

A mixture of $Pd(PPh_3)_4$ (4 mol %), K_2CO_3 (1.7 equiv), and NaO-*t*-Bu (1.7 equiv) was added to a solution of the amine (1.0 equiv) in toluene, and the flask was heated to 100 °C for 16 h. After cooling to RT, the solution was poured into a separatory funnel containing H_2O and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo. The indoline product was partially purified by flash chromatography, and a portion of the material (typically ca. 75%) was used directly in the next step.

The indoline derivative (1.0 equiv) was treated with 10 mol % (by weight) Pd/C (10 mol %) and ammonium formate (10.0 equiv) in MeOH. After heating to reflux for 2 h, the solution was cooled to RT and filtered through Celite. The solvent was removed using a rotary evaporator, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography.

Table 1, Entry 1: 3-[4-[(Triisopropylsilyl)oxy]butyl]-7-methylindole. The title compound (80 mg, 45% from Cp_2TiCl_2) was prepared as a colorless oil using general procedure A and was purified by flash chromatography (4:1 then 2:1 hexane/CH_2Cl_2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1 H), 7.46 (d, J = 7.5 Hz, 1 H), 7.07−6.95 (m, 3 H), 3.72 (t, J = 6.3 Hz, 2 H), 2.77 (t, J = 7.5 Hz, 2 H), 2.47 (s, 3 H), 1.86−1.72 (m, 2 H), 1.71−1.59 (m, 2 H), 1.20−1.04 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 127.2, 122.4, 120.7, 120.1, 119.3, 117.6, 116.8, 63.3, 33.0, 26.4, 25.1, 18.1, 16.5, 12.1; IR (neat) 3422,

2941, 2865, 1459, 1106, 882 cm^{-1}. Anal. Calcd for $C_{22}H_{37}NOSi$: C, 73.48; H, 10.37. Found: C, 73.74; H, 10.59.

Table 1, Entry 2: 7-Methyl-3-[2-phenyl-2-[(triisopropylsilyl)oxy]-ethyl]indole. The title compound (0.10 g, 40% from Cp_2TiCl_2) was prepared as a colorless oil using general procedure A and was purified by flash chromatography (2:1 hexane/Et_2O):$[\alpha]^{25}_D = +23.9$ (*c* 1.09, $CHCl_3$); HPLC Chiralcel OD 25 cm × 0.46 cm column (Daicel Chemical Ind., Ltd.), eluent 99:1 hexane/isopropyl alcohol, flow rate 0.5 mL/min, detection UV 254 nm, retention time for (*S*)-enantiomer 23.6 min, retention time for (*R*)-enantiomer 25.5 min, optical purity 67% ee; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (br s, 1H), 7.35−6.90 (m, 8H), 6.56 (m, 1H), 5.01 (dd, J = 5.4, 8.0 Hz, 1 H), 3.31 (dd, J = 5.4, 14.0 Hz, 1 H), 3.05 (dd, J = 8.0, 14.0 Hz, 1 H), 2.43 (s, 3 H), 1.10−0.85 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.6, 127.6, 126.8, 126.5, 122.8, 122.2, 119.9, 119.3, 116.6, 112.8, 75.7, 37.5, 18.0, 17.9, 16.5, 12.4; IR (neat) 3425, 2942, 2865, 1460, 1090, 1065, 882 cm^{-1}. Anal. Calcd for $C_{26}H_{37}NOSi$: C, 76.60; H, 9.15. Found: C, 76.79; H, 8.96.

Table 1, Entry 3: 3-Butyl-7-methylindole. The title compound (47 mg, 54% from Cp_2TiCl_2) was prepared as colorless needles using general procedure A and was purified by flash chromatography (3:1 hexane/CH_2Cl_2): mp 39.5−40.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.10−6.95 (m, 3 H), 2.75 (t, J = 7.0 Hz, 2 H), 2.48 (s, 3 H), 1.75−1.60 (m, 2 H), 1.42 (sextet, J = 7.0 Hz, 2 H), 0.95 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 127.2, 122.3, 120.7, 120.1, 119.3, 117.7, 116.8, 32.4, 25.0, 22.7, 16.6, 14.0; IR (KBr) 3433, 2960, 2920, 2855, 1464, 1430, 1100, 1066, 788, 745 cm^{-1}. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.40; H, 9.33.

Table 1, Entry 4: 3-Butyl-4,7-dimethylindole. The title compound (88 mg, 37% from Cp_2TiCl_2) was prepared as colorless needles using general procedure A and was purified by flash chromatography (3:1 hexane/CH_2Cl_2): mp 73.5−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1 H), 6.94 (s, 1 H), 6.85 (d, J = 7.1 Hz, 1 H), 6.75 (d, J = 7.1 Hz, 1 H), 2.90 (t, J = 7.4 Hz, 2 H), 2.68 (s, 3 H), 2.42 (s, 3 H), 1.67 (m, 2 H), 1.47 (sextet, J = 7.3 Hz, 2 H), 0.97 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 128.6, 125.5, 122.2, 120.9, 118.8, 117.7, 33.7, 26.9, 22.6, 20.0, 16.2, 14.0; IR (KBr) 3425, 2953, 2856, 1511, 803 cm^{-1}. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.76; H, 9.79.

Table 1, Entry 5: 3-Butylnaphthoindole. The title compound (43 mg, 35% from Cp_2TiCl_2) was prepared as colorless needles using general procedure A and was purified by flash chromatography (4:1 hexane/CH_2Cl_2): mp 132−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.6 (br s, 1H), 7.98 (d, J = 8.4 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 9.3 Hz, 1 H), 7.55−7.38 (m, 3 H), 7.06 (m, 1H), 2.83 (t, J = 7 Hz, 2 H), 1.80−1.64 (m, 2 H), 1.45 (sextet, J = 7.2 Hz, 2 H), 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 130.8, 130.4, 128.8, 125.3, 123.7, 123.4, 121.8, 119.9, 119.3, 119.2, 119.0, 32.7, 24.9, 22.6, 14.0; IR (KBr) 3411, 2957, 2915, 2855, 1524, 1452, 1392, 811 cm^{-1}. Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67. Found: C, 86.34; H, 7.83.

Table 1, Entry 6: 3-Butyl-4-methoxy-7-methylindole. The title compound (0.12 g, 18% from Cp_2TiCl_2) was prepared as a colorless oil using general procedure A and was purified by flash chromatography (10:1 hexane/ethyl acetate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (br s, 1 H), 6.86 (m, 2 H), 6.40 (d, J = 7.9 Hz, 1 H), 3.89 (s, 3 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.39 (s, 3 H), 1.66 (m, 2 H), 1.42 (sextet, J = 7.3 Hz, 2 H), 0.95 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 137.4, 122.4, 119.5, 118.5, 113.0, 99.3, 97.3, 55.2, 42.0, 33.4, 26.5, 22.6, 14.1; IR (neat) 3470, 2958, 2861, 1604, 1515, 1264 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.44; H, 9.04.

7-Methyl-3-[2-(7-methyl-3-indolyl)ethyl]indole (3). The title compound (26 mg, 16% from 1,5-hexadiene) was prepared as colorless needles from Cp_2TiCl_2 (2 mol equiv) and 1,5-hexadiene (1 mol equiv) using general procedure A and was purified by flash chromatography (2:1 hexane/acetone): mp 225−226 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 9.90 (br s, 2 H), 7.49 (d, J = 7.1 Hz, 2 H), 7.15 (m, 2 H), 7.05−6.85 (m, 4 H), 3.15 (s, 4 H), 2.49 (s, 6 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 137.2, 128.5, 122.7, 122.6, 122.4, 121.3, 119.7, 117.3, 27.4, 17.0; IR (KBr) 3406, 2880, 2838, 2536, 1492, 1458, 1436, 1064 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99. Found: C, 83.55; H, 7.28.

2-Methyl-6-vinyl-*N*-benzylaniline (7). A mixture of $Pd_2(dba)_3$ (41 mg, 2 mol %), P(*o*-tolyl)$_3$ (84 mg, 6 mol %), and NaO-*t*-Bu (0.30 g, 3.16 mmol) was added to a solution of the dibromide **4** (0.63 g, 2.26 mmol) in toluene, and the flask was heated to 80 °C for 16 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_2O and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo. The product was purified by flash chromatography (20:1 hexane/ethyl acetate) to give 0.19 g (38%) of a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.62−7.56 (m, 6 H), 7.36−7.30 (m, 2 H), 7.19 (t, J = 7.5 Hz, 1 H), 5.93 (dd, J = 1.6, 19.2 Hz, 1 H), 5.54 (dd, J = 1.6, 10.8 Hz, 1 H), 4.43 (s, 2 H), 3.63 (br s, 1 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 140.4, 134.6, 130.8, 130.1, 129.4, 128.5, 127.8, 127.3, 125.2, 122.2, 114.4, 54.0, 18.0; IR (neat) 3367, 3028, 2928, 1591, 1464, 700 cm^{-1}.

Table 2, Entry 1: 7-Methylindole.[16] Cp_2TiCl_2 (2.61 g, 10.48 mmol) in toluene (70 mL) was employed according to general procedure B. The indole product was purified by flash chromatography (10:1 hexane/ethyl acetate) to yield 0.56 g of a white solid (40% from Cp_2TiCl_2): mp 80−82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.20 (m, 1 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.04 (d, J = 7.3 Hz, 1 H), 6.60 (s, 1 H), 2.52 (s, 3 H).

Table 2, Entry 2: 4-Methoxy-7-methylindole. Cp_2TiCl_2 (0.93 g, 3.75 mmol) in toluene (25 mL) was employed according to general procedure B. The indole product was purified by flash chromatography (10:1 hexane/ethyl acetate) to yield 0.21 g of a colorless oil (34% from Cp_2TiCl_2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1 H), 7.11 (s, 1 H), 6.94 (d, J = 7.7 Hz, 1 H), 6.72 (s, 1 H), 6.50 (d, J = 7.7 Hz, 1 H), 3.98 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 136.6, 122.6, 122.5, 118.0, 113.3, 100.3, 99.6, 55.4, 16.0; IR (KBr) 3394, 3105, 2962, 1524, 1500, 1262 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88. Found: C, 74.59; H, 7.22.

Table 2, Entry 3: 3-Butyl-7-methoxyindole. The title compound (65 mg, 43% from Cp_2TiCl_2) was prepared as a colorless oil using general procedure C and was purified by flash chromatography (4:1 hexane/CH_2Cl_2): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.22 (d, J = 7.8 Hz, 1 H), 7.02 (t, J = 7.8 Hz, 1 H), 6.9 (m, 1 H), 6.62 (d, J = 7.8 Hz, 1 H), 3.93 (s, 3 H), 2.73 (t, J = 7.3 Hz, 2 H), 1.75−1.55 (m, 2 H), 1.40 (sextet, J = 7.2 Hz, 2 H), 0.94 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 129.0, 126.8, 120.6, 119.4, 117.5, 111.8, 101.7, 55.3, 32.4, 25.0, 22.6, 14.0; IR (neat) 3416, 2952, 2927, 2854, 1577, 1498, 1446, 1373, 1258, 1077, 1040 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.08; H, 8.56.

Table 2, Entry 4: 3-[8-(*tert*-Butoxycarbonyl)octyl]-7-methylindole. The title compound (86 mg, 33% from Cp_2TiCl_2) was prepared as colorless needles using general procedure C and was purified by flash chromatography (3:1 hexane/Et_2O): mp 57−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (br s, 1H), 7.46 (d, J = 7.8 Hz, 1 H), 7.08−6.95 (m, 3 H), 2.73 (t, J = 7.2 Hz, 2 H), 2.48 (s, 3 H), 2.19 (t, J = 6.9 Hz, 2 H), 1.76−1.50 (m, 4 H), 1.44 (s, 9 H), 1.42−1.20 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 135.9, 127.1 122.3, 120.7, 120.1, 119.2, 117.6, 116.7, 79.9, 35.6, 30.2, 29.5, 29.3, 29.1, 28.1, 25.3, 25.1, 16.6; IR (KBr) 3356, 2917, 2849, 1718, 1466, 1160 cm^{-1}. Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 77.15; H, 9.95.

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