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A Flexible Synthesis of 2,3-Disubstituted Indoles from Aminobenzyl Phosphonium Salts. A Direct Synthesis of Rutaecarpine

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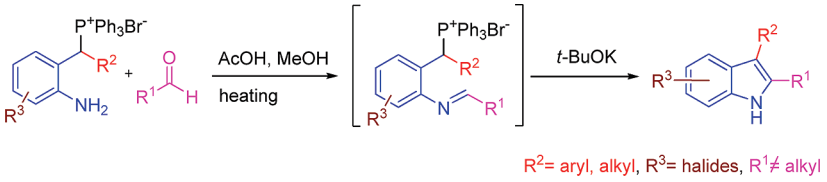

The reaction of substituted (2-aminobenzyl)triphenylphosphonium bromides with aromatic aldehydes or α,β-unsaturated aldehydes constitutes a new synthesis of 2,3-disubstitued indoles in high yields. The adduct from 4-oxo-3,4-dihydroquinazoline-2-carbaldehyde was an advanced intermediate in the synthesis of several rutaecarpines.

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Introduction

Although a number of versatile indole syntheses have been reported, the development of new methods for the synthesis of indoles remains an active area of research.[1] This is in part due to the continual emergence of novel biologically active indole-containing natural products, such as the recently discovered indoles **1**−**3**, and also due to the development of useful synthetic pharmaceuticals bearing the indole subunit (Figure 1).[2] Compound **1** exhibits potent immunomodulatory and cytotoxic activity.[3] Indole **2** was active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[4] Compound **3** shows settlement inhibition of barnacle larvae (*Balanus improVisus*) with an EC_{50} value of 15 nM.[5]

Many widely used indole syntheses have the retrosynthetic analysis represented by disconnection A (Scheme 1). These reactions include the Fischer indole synthesis,[6] the Japp−Klingemann route,[7] the Gassman indole synthesis,[8] the Sugasawa indole synthesis, and the Bischler indole[9] synthesis. When G is a bromide or iodide, this is the starting material for several organopalladium-mediated synthetic routes to indoles.[10]

In contrast, relatively few indole syntheses are represented by disconnection B. Several groups have reported a reductive cyclization of *o*-ketoamides.[11,12] The Madelung reaction

(1) (a) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1. (b) Sundberg, R. J. *Prog. Heterocycl. Chem.* **1989**, *1*, 111. (c) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804. (d) Gribble, G. W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Ed.; Pergamon Press: Oxford, UK, **1996**; Vol. 2, p 207. (e) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, *15*, 327. (f) Sundberg, R. J. *Indoles*; Academic Press: New York, **1996**. (g) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (h) Mori, H.; Yoshimi, N. *Mutat. Res.* **2001**, *480*, 201. (i) Tokuyama, H.; Fukuyama, T. *Kagaku Kogyo* **2001**, *52*, 416. (j) Lobo, A. M.; Prabhakar, S. *J. Heterocycl. Chem.* **2002**, *39*, 429. (k) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115.

(2) (a) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Baldwin, J. E., Williams, R. M., Eds.; Pergamon Press: New York, 2000; Vol. 20, pp 73−181. (b) Glennon, R. A. J. Med. Chem. 1987, 33, 1.

(3) (a) Don, M. J.; Lewis, F. V.; Wang, S. Y.; Tsai, M. W.; Ueng, Y. F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2535. (b) Tseng, J. C.; Don, M. J.; Lewis, F. V.; Wang, S. Y.; Ueng, Y. F. *Yaowu Shipin Fenxi* **2007**, *15*, 480.

(4) McArthur, K. A.; Mitchell, S. S.; Tsueng, G.; Rheingold, A.; White, D. J.; Grodberg, J.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod.* **2008**, *71*, 1732.

(5) Hedner, E.; Sjoegren, M.; Hodzic, S.; Andersson, R.; Goeransson, U.; Jonsson, P. R.; Bohlin, L. *J. Nat. Prod.* **2008**, *71*, 330.

(6) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241.

(7) Japp, F. R.; Klingemann, F. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2942.

(8) Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590.

(9) (a) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578. (b) Bischler, A.; Brion, H. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2860.

(10) (a) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215. (b) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V.; Thorntorn-Pett, M. *Tetrahedron* **1998**, *54*, 2595. (c) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (d) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (e) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (f) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (g) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (h) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250. (i) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (j) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (k) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (l) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

(11) Fan, X. S.; Zhang, X. Y.; Zhang, Y. M.; Qu, G. R. *Chin. Chem. Lett.* **2004**, *15*, 518.

(12) Fan, X.; Zhang, Y. *Tetrahedron* **2003**, *59*, 1917.

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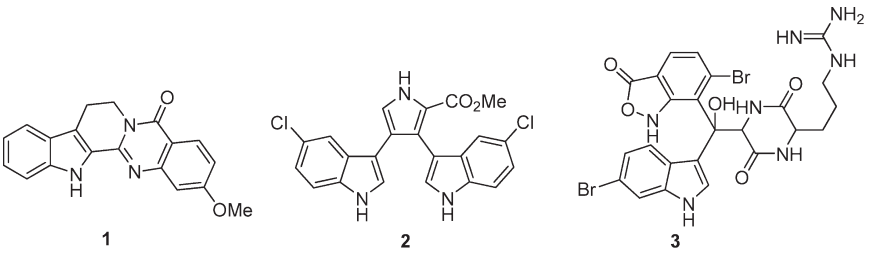
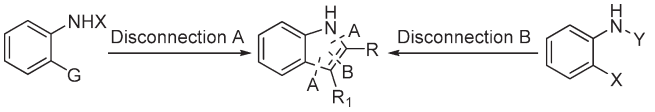
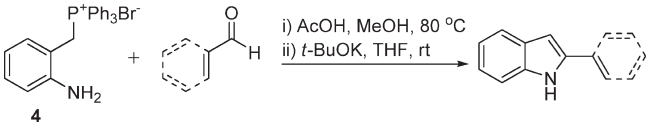


FIGURE 1. Recent found indole derivatives.

SCHEME 1



SCHEME 2



involves cyclization of the dianion of an anilide at elevated temperature.[13] Various cyclizations using intramolecular Claisen condensations and Wittig reactions have been reported.[14] Two groups have employed radical-mediated conjugate additions.[15,16]

Despite the fact that these reactions are synthetically useful, they suffer from several disadvantages: (i) high temperatures and long reaction times (above 125 °C and 12 h), (ii) expensive transition metal catalysts, and (iii) multistep and moderate yields, as well as high sensitivity to moisture. We recently reported a direct synthesis of 2-substituted indoles by way of a novel six-electron electrocyclic closure of the imine derived from commercially available phosphonium salt **4** (Scheme 2).[17] Our method is depicted in Scheme 2 and proceeds under mild conditions with use of readily available reagents in high yield (81−95%) in one pot. Herein we wish to expand this electrophilic cyclization strategy as a practical and convenient synthetic method for the synthesis of 2,3-disubstituted indoles.

Results and Discussion

Initially, we synthesized a set of phosphonium salts **5a**−**c** bearing substituents on the benzylic carbon. Successful reactions of these phosphonium salts would provide a useful synthesis of 2,3-disubstituted indoles. Phosphonium salts **5a**, **5b**, and **5c** were readily prepared by the reduction of the commercially available aromatic ketones, followed by treatment of the resulting amino alcohols with 1 equiv of triphenylphosphine hydrobromide (Scheme 3). The functional group R_1 will be at the indole 3-position after the ring closure. Compound **5a** will be the precursor for 2,3-disubstituted indoles with an aryl group at the 3-position and **5b** will be the precursor for alkyl substitution at the 3-position. Compound **5c** will also probe the compatibility of halogen substitution.

Initial studies were aimed at finding the optimal reaction conditions for acid-catalyzed imine formation of the anilines **5** from aromatic aldehydes. Our investigation began with the reaction of phosphonium salt **5a** and benzaldehyde (Scheme 4). The reaction was first attempted with 1 equiv of phosphonium salt (**5a**), 1 equiv of benzaldehyde, and acetic acid (0.4 equivalent) as the catalyst in boiling MeOH. This reaction provided almost quantitative yield of the desired imine according to ^{1}H NMR. The imine was not isolated but was immediately dissolved in THF and treated with 1.6 equiv of potassium *tert*-butoxide. The second step is the six-electron electrocyclic closure. This step is facile even at −78 °C and efficiently generated the desired 2,3-diphenyl indole **6** in 92% isolated yield after 1 h at ambient temperature. The solvent has to be THF because methanol reacts with the imine intermediate.

Microwave-assisted organic synthesis is an efficient method for the synthesis of heterocyclic compounds.[18,19] As opposed to conventional heating, application of microwave energy has the major advantage of shorter reaction times because of the rapid core heating associated with microwaves. Therefore, reactions frequently exhibit cleaner product profiles and use minimal quantities of solvent. Many reviews have been published that give more detail about this new application.[20] This prompted us to synthesize imines under microwave conditions. The conditions we applied in a CEM microwave oven were similar to the conventional procedure: the phosphonium salt **5a** and benzaldehyde with a catalytic amount of acetic acid were dissolved in methanol and the solution was heated in a sealable tube to 80 °C (compare to 65 °C in conventional conditions). As expected, the reaction time was reduced dramatically. The imine formation that took 12 h by conventional heating was speeded up to 10 min. After the base-mediated step, we obtained the 2,3-disubstituted indole in 93% yield. The mild reaction conditions as

(13) Madelung, W. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 1128.
(14) (a) Le Corre, M.; Hercouet, A.; Le Stanc, Y.; Le Baron, H. *Tetrahedron* **1985**, *41*, 5313. (b) Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034. (c) Eitel, M.; Pindur, U. *Synthese* **1989**, *5*, 364. (d) Kuehler, T. C.; Swanson, M.; Christenson, B.; Klintenberg, A.; Lamm, B.; Faegerhag, J.; Gatti, R.; Oelwegaard-Halvarsson, M.; Shcherbuchin, V.; Elebring, T.; Sjoestroem, J. *J. Med. Chem.* **2002**, *45*, 4282. (e) Tao, M.; Park, C. H.; Bihovsky, R.; Wells, G. J.; Husten, J.; Ator, M. A.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 938.
(15) Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429.
(16) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246.
(17) Kraus, G. A.; Guo, H. T. *Org. Lett.* **2008**, *10*, 3061.
(18) Kaddar, H.; Hamelin, J.; Benhaoua, H. *J. Chem. Res.* **1999**, 718.
(19) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95.
(20) (a) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

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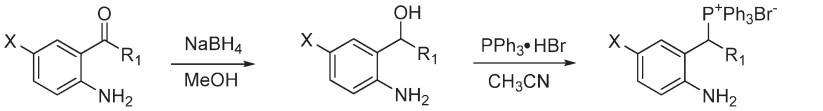
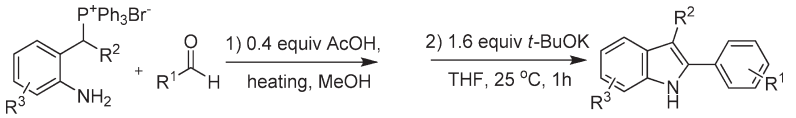
SCHEME 3



5a: R_1=Ph, X=H (95%)
5b: R_1=Me, X=H (92%)
5c: R_1=Ph, X=Cl (95%)

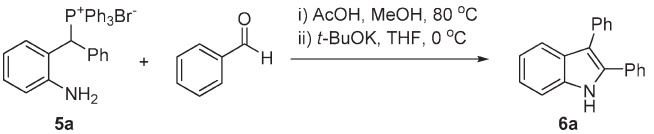
TABLE 1. Reaction of 5a−c with Aldehydes To Generate 2,3-Disubstituted Indoles[a]



entry	phosphonium salts	aldehydes	product		isolated yield (%)[b]
1	**5a**			**6a**	93 (92)[c]
2				**6b**	100
3				**6c**	84
4				**6d**	90
5				**6e**	86
6				**6f**	100
7				**6g**	45
8				**6h**	88
9				**6i**	96
10				**6j**	56
11	**5b**			**6k**	97 (95)[c]
12				**6l**	85
13				**6m**	84
14				**6n**	79
15				**6o**	72
16				**6p**	88
17				**6q**	78
18	**5c**			**6r**	100 (96)[c]
19				**6s**	92
20				**6t**	96
21				**6u**	100
22				**6v**	93

[a] Reaction conditions: (i) phosphonium salt **4** (1 mmol), aldehyde (1 mmol), AcOH (0.4 mmol), methanol (2 mL); (ii) *t*-BuOK (1.6 mmol), THF (2 mL). [b] Isolated yield. [c] Conventional thermal yield.

SCHEME 4



5a **6a**

well as the high yield of this reaction encouraged us to extend this methodology to a range of aldehydes.

Next, the scope and limitations of this reaction were examined. Table 1 summarizes the results of reactions of phosphonium salts **5a−c** with an array of aldehydes under the optimized reaction conditions. We tried a few examples using both conventional thermal and microwave conditions (entries 1, 11, and 18). These results show that the reaction proceeds very efficiently under both thermal and microwave conditions but the latter conditions are more efficient. The cyclization proceeds smoothly when the substituents on the α-position of the phosphonium salt are aryl or alkyl. However, the indole formed by the cyclization of phosphonium salt **5a** with methyl 4-formylbenzoate (entry 7) gave a slightly lower yield (45%). The reason is that this compound is unstable during column chromatography. The only way that we could purify the compound was to do a short column to remove most of the triphenylphosphine and then recrystallize the crude material to obtain pure indole **6h**.

A wide range of aldehydes react effectively with phosphonium salts **5a**, **5b**, and **5c**, including a variety of electron-

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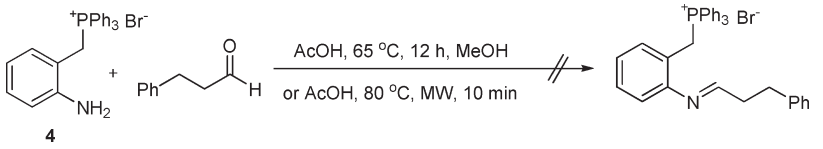
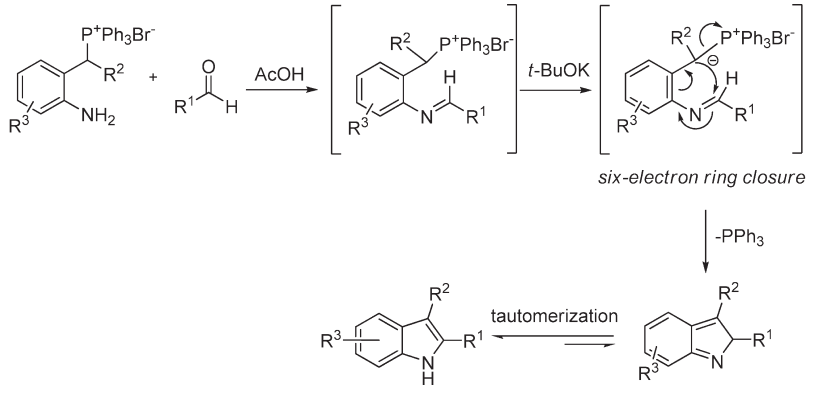
SCHEME 5



SCHEME 6



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donating and electron-withdrawing substituents, such as aromatic ethers, halides, ester, hydroxy, and aryl groups (entries 2−7, 12−15, and 19−20). The yield range is from 72% to 100% for most of the cases. A series of heterocyclic aldehydes have been tried with this method and undergo smooth cyclization at room temperature to afford the corresponding 2,3-disubstituted indoles in excellent yield (entries 9, 10, 16, 17, 21, and 22). In addition, we also expanded this methodology to α,β-unsaturated aldehydes (entries 8 and 19) which also gave high yields. Unfortunately, alkyl aldehydes such as hydrocinnamaldehyde and heptanal did not form the imine intermediates with phosphonium salt **4** under either conventional thermal or microwave conditions (Scheme 5). This may be because the alkyl aldehydes are not as stable as the aryl or α,β-unsaturated aldehydes under the acidic conditions and undergo an aldol reaction. Further studies are still ongoing.

We believe that these cyclizations proceed by imine formation, followed by six-electron ring closure, to form the desired 2,3-disubstituted indoles as shown in Scheme 6. The success of this reaction may be due to several factors: (1) the imine intermediates are conjugated with the aromatic system, which makes them very good acceptors, and (2) the triphenylphosphine group is a bulky leaving group and readily eliminates.

Rutaecarpine (**7**) is an indolopyridoquinazolinone alkaloid isolated from *Evodia rutaecarpa*, which has shown antithrombotic, anticancer, anti-inflammatory, analgesic, and antiobesity activity (Figure 2). It has been synthesized by several groups.[21] Recently, biologically active "hybrid" analogues, nor-rutaecarpines **8** and **9**, have been isolated and synthesized.[22] The studies show that these compounds exhibit activity against a range of ailments including rheumatism, influenza, leukemia, and hepatitis.[23] The indole **10** is an advanced intermediate for these rutaecarpine analogues. Lee and co-workers have reported a synthesis of compound **10** in four steps in 31% overall yield.[24] Recently, Bubenyak and co-workers reported another synthesis of intermediate **10** by a Fischer indole synthesis. It required four steps and afforded a 48% overall yield.[22c]

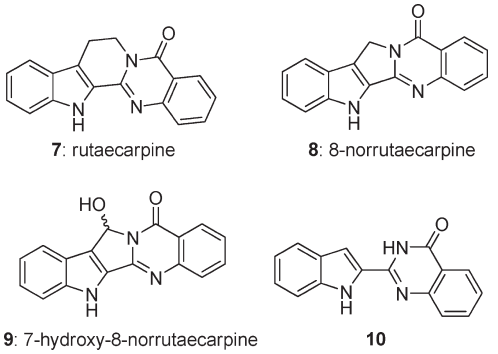


FIGURE 2. Rutaecarpine derivatives.

Our route begins with known aldehyde **11**, which can be synthesized in one step from commercially available

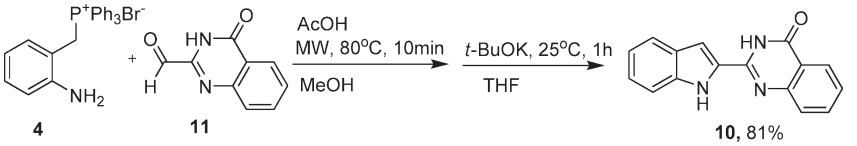
(21) For synthesis: (a) Lingam, Y.; Bhowmik, D. P.; Srinivas, G.; Islam, A.; Rao, D. M. *Nat. Prod.* **2007**, *3*, 58. (b) Lee, C. S.; Liu, C. K.; Chiang, Y. L.; Cheng, Y. Y. *Tetrahedron Lett.* **2008**, *49*, 481. (c) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (d) Bowman, W. R.; Elsegood, M. R. J.; Stein, T.; Weaver, G. W. *Org. Biomol. Chem.* **2007**, *5*, 103. (e) Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 10645. For biology property: (f) Dai, Z.; Xiao, J.; Liu, S.-Y.; Cui, L.; Hu, G.-Y.; Jiang, D.-J. *Neuropharmacology* **2008**, *55*, 1307. (g) Hibino, T.; Yuzurihara, M.; Terawaki, K.; Kanno, H.; Kase, Y.; Takeda, A. *J. Pharmacol. Sci.* **2008**, *108*, 89. (h) Li, D.; Peng, J.; Xin, H. Y.; Luo, D.; Zhang, Y. S.; Zhou, Z.; Jiang, D. J.; Deng, H. W.; Li, Y. J. *Peptides* **2008**, *29*, 1781.

(22) (a) Yang, L.-M.; Chen, C. F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 465. (b) Dallavalle, S.; Merlini, L.; Beretta, G. L.; Tinelli, S.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5757. (c) Bubenyak, M.; Palfi, M.; Takacs, M.; Beni, S.; Szoko, E.; Noszal, B.; Kokosi, J. *Tetrahedron Lett.* **2008**, *49*, 4937.

(23) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.

(24) Lee, E. S.; Son, J. K.; Na, Y. H.; Jahng, Y. *Heterocycl. Commun.* **2004**, *10*, 325.

SCHEME 7



3-methylquinoxazoline.[25] The indole **10** can be generated from aldehyde **11** and commercial available phosphonium salt **4** in 81% yield (Scheme 7).

Conclusions

In conclusion, we have developed a very efficient synthesis of 2,3-disubstituted indoles by a two-step approach in one pot involving imine formation and six-electron ring closure, followed by a 1,5-hydrogen shift. These reactions proceed under very mild conditions and remarkably short reaction times. A wide range of aryl or α,β-unsaturated aldehydes undergo this process in excellent yield. The adduct from 4-oxo-3,4-dihydroquinazoline-2-carboxaldehyde is an advanced intermediate in the synthesis of several rutaecarpine analogues.

Experimental Section

General Procedure for the Synthesis of 2,3-Disubstituted Indoles from Substituted 2-Aminobenzyl Phosphonium Salts. In a 10 mL microwave reaction vessel (CEM Discover System) equipped with a magnetic stir bar, phosphonium salt **5a** (262 mg, 0.5 mmol), the aldehyde (0.5 mmol), and glacial acetic acid (11.4 μL, 0.2 mmol) were added to 3 mL of distilled methanol. The vial was capped properly and placed in the microwave. Microwave irradiator was carried out at 80 °C for 10 min (temperature fixed). After the vial was cooled to room temperature, methanol was removed under vacuum. All methanol must be removed before the next step. THF (4 mL) was added to the mixture and 0.8 mL of a 1 M *t*-BuOK solution in THF was added dropwise. The resulting mixture was stirred at 25 °C under argon for 1 h. The saturated NH_4Cl solution (10 mL) was added to quench the reaction. The aqueous layer was extracted with ethyl acetate (3×10 mL). The organic layers were combined and washed with brine (2 × 10 mL). The organic layer was separated, dried with $MgSO_4$, and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography by using a mixture of ethyl acetate and hexanes as the eluent.

2-(3-Hydroxyphenyl-4-methoxy)-3-phenylindole (6f). The product was purified by short chromatography on silica gel (R_f 0.35 in 80% hexanes/20% EtOAc). The product was obtained as a yellow solid (157 mg, 100% yield): mp 72−74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.34−7.54 (d, J = 8.0 Hz, 1H), 7.51−7.53 (d, J = 6.8 Hz, 2H), 7.19−7.45 (m, 5H), 7.08−7.09 (d, J = 2.0 Hz, 1H), 6.90−6.92 (m, 1H), 6.72−6.74 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 145.7, 135.9, 135.4, 134.2, 130.3, 128.9, 128.7, 126.3, 126.1, 122.5, 120.7, 120.4, 119.6, 114.5, 114.3, 111.1, 111.0, 55.98; HRMS electrospray (*m*/*z*) calcd for $C_{21}H_{17}NO_2$ 315.1259, found 315.1264.

4-(3-Phenylindol-2-yl)benzoate (6g). The product was purified by short chromatography on silica gel (R_f 0.30 in 90% hexanes/10% EtOAc). The product was obtained by recrystallization from the mixture of CH_2Cl_2 and hexane as a white solid (74 mg, 45% yield): mp 192−193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.91−7.93 (d, J = 8.4 Hz, 2H), 7.58−7.60 (d, J = 8.4 Hz, 2H), 7.49−7.51 (d, J = 8.4 Hz, 2H), 7.29−7.43 (m, 5H), 7.19−7.23 (m, 1H), 7.05−7.08 (t, J = 7.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 137.6, 137.0, 135.3, 133.1, 130.3, 129.8, 128.6, 128.4, 126.9, 123.2, 120.5, 119.4, 115.5, 112.2, 52.6; HRMS electrospray (*m*/*z*) calcd for $C_{22}H_{17}NO_2$ 327.1259, found 327.1263.

3-Phenyl-2,3′-biindole (6i). The product was purified by short chromatography on silica gel (R_f 0.15 in 75% hexanes/25% EtOAc). The product was obtained as a yellow solid (117 mg, 76% yield): mp 202−204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 11.30 (s, 1H), 7.59−7.61 (d, J = 8.0 Hz, 1H), 7.39−7.50 (m, 5H), 7.29−7.33 (t, J = 7.6 Hz, 2H), 7.05−7.20 (m, 5H), 6.83−6.87 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.7, 136.6, 130.8, 129.6, 128.9, 128.3, 125.9, 125.7, 125.5, 122.1, 121.6, 120.4, 120.0, 119.8, 118.4, 112.6, 112.2, 111.7, 108.2; HRMS electrospray (*m*/*z*) calcd for $C_{22}H_{16}N_2$ 308.1313, found 308.1319.

5-Chloro-3-phenyl-2,3′-biindole (6v). The product was purified by short chromatography on silica gel (R_f 0.15 in 60% hexanes/40% EtOAc). The product was obtained as a light yellow solid (159 mg, 93% yield): mp 220−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.6 (s, 1H), 11.5 (s, 1H), 7.43−7.59 (m, 6H), 7.32−7.36 (d, J = 7.6 Hz, 2H), 7.10−7.24 (m, 4H), 6.88−6.92 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.8, 136.0, 135.1, 133.0, 129.7, 129.6, 129.0, 126.2, 126.1, 125.7, 124.6, 122.1, 121.4, 120.5, 119.8, 117.5, 113.2, 112.3, 112.2, 107.6; HRMS electrospray (*m*/*z*) calcd for $C_{22}H_{15}ClN_2$ 342.0924, found 342.0928.

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Supporting Information Available: General experimental procedures and spectral data for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) Khalil, Z. H.; Koraiem, A. I. M.; El-Maghraby, M. A.; Abu-El-Hamd, R. M. *J. Chem. Tech. Biotech.* **1986**, *36*, 379.

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