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Total Synthesis of 8,14-Dihydromorphinandienone Alkaloids

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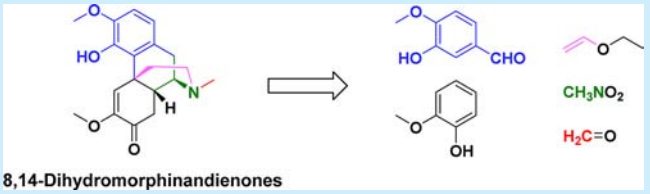
Supporting Information

ABSTRACT: A collective synthesis of 8,14-dihydronorsalutaridine, 8,14-dihydrosalutaridine, norisosinomenine, and isosinomenine is reported. The strategy provides direct access to the correct oxidation level of the products. The combination of an organocatalyst guanidine superbase, a tertiary amine base, and a dehydrating agent was necessary for the successful Henry–Michael–dehydration cascade to form the phenanthrene motif. The required selective aliphatic nitro reduction could only be achieved under heterogeneous transfer–hydrogenation conditions.



Historically, biogenetic *o,p*-phenolic oxidative coupling has been an inefficient but reliable route to morphinandienone alkaloids.[1] A related group of compounds, the 8,14-dihydromorphinandienone alkaloids, constitute a lesser known subset. Five members of this group with the general structure **A** have been isolated, Figure 1.

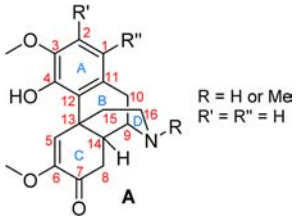


Figure 1. General subset structure.

The closest congeners of these molecules are the well-known norsalutaridine, salutaridine, norsinoacutine, and sinoacutine in which C8–C14 is a double bond, Figure 2.

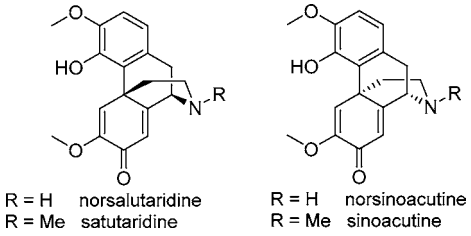


Figure 2. Morphinandienones.

The five known alkaloids belonging to subset **A** are 8,14-dihydronorsalutaridine,[2] 8,14-dihydrosalutaridine,[3] isosinomenine,[4] milonine,[5] and ocobotrine,[6] Figure 3.

Salutaridine and sinoacutine have been synthesized via biomimetic *o,p*-phenolic coupling from reticuline, which produced the dienone motif in the C-ring.[7] Herein, we wish

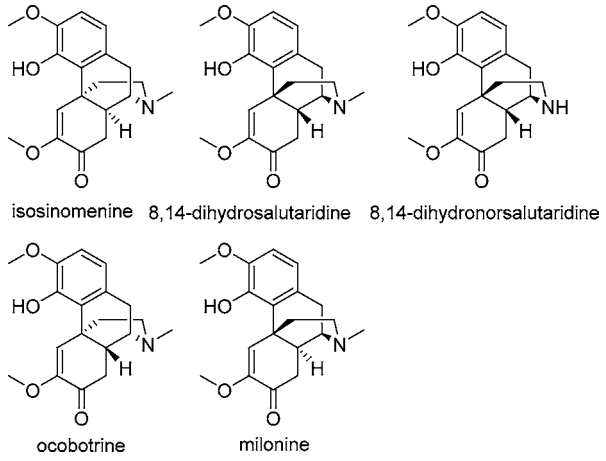


Figure 3. 8,14-Dihydromorphinandienone subset.

to report the first total synthesis of the alkaloids 8,14-dihydronorsalutaridine, 8,14-dihydrosalutaridine, norisosinomenine, and isosinomenine at the correct "8,14-dihydro" oxidation level. Key structures are shown in the retrosynthesis, Scheme 1, along with the actual synthesis, Scheme 2.

Preparation of biaryl **4** via coupling of C12 and C13 began from commercially available 4-bromoguaiacol **1** and bromoisovanillin. Protection of phenol **1** using TBSCl and imidazole in DCM at 0 °C gave **2** in 98% yield. Treatment of **2** with BuLi in THF at −78 °C followed by quenching with $(^{i}PrO)_3B$ provided the boroxine **3** in 80% yield. Suzuki coupling of bromoisovanillin and trimer **3** gave biaryl **4** in 89% yield. This strategy effectively replaced the biogenetic *o,p*-phenolic coupling with a Suzuki reaction. Bromination of ethyl vinyl ether (EVE) in DCM at 0 °C generated the dibromide alkylating agent in situ. In the presence of DIEA, **4** was alkylated by the dibromide to give acetal **5** in 98% yield. Treatment of **5** with CsF in DMF at

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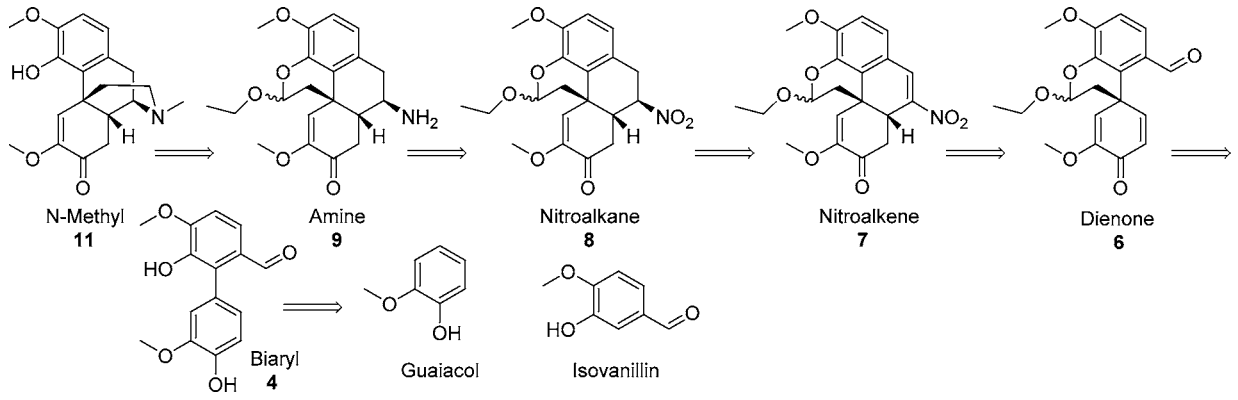
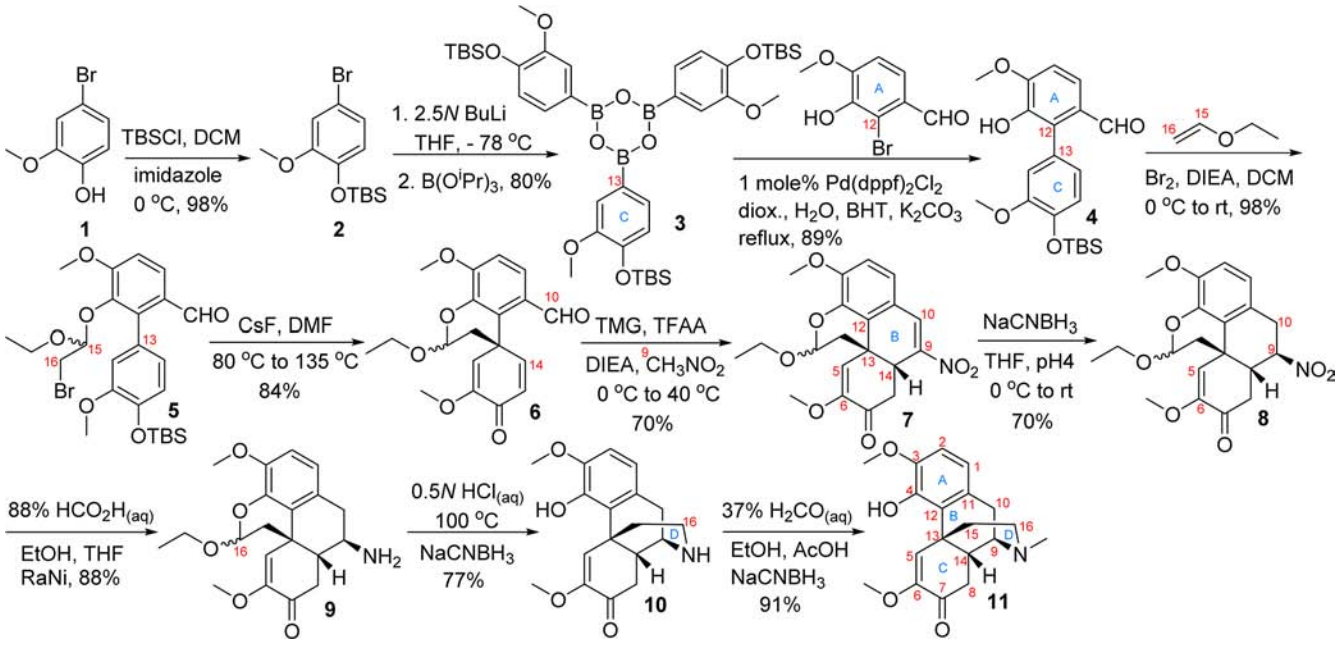
Scheme 1. Retrosynthesis



Scheme 2. Synthesis



135 °C (intramolecular *p*-phenolic alkylation) gave diastereomeric dienone **6** in 84% yield (Figure 4, structures by X-ray).

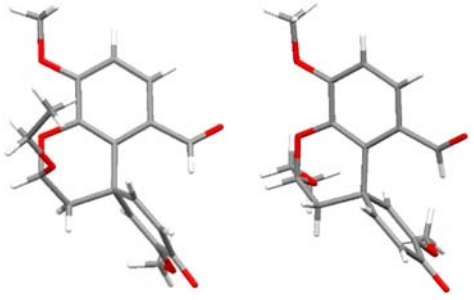


Figure 4. Dienone (**6a,b**) X-rays.

Preparation of the nitroalkene diastereomers **7** posed a significant challenge. The cascade consisted of three steps: a Henry[8] reaction between nitromethane C9 and the aldehyde C10, an intramolecular Michael addition of C9 to C14, and a dehydration reaction to form the double bond between C9 and C10.

Initially, $NH_4OAc/AcOH$ in refluxing CH_3NO_2 provided less than 10% yield. This was in sharp contrast to the 97% yield reported by Magnus[9] using the analogous substrate without the C6 methoxy enol ether. Reagents that are usually effective, such as γ-Al_2O_3,[10] ionic liquids,[11] Amberlysts,[12] and phase-transfer catalysts;[13] dehydrating agents such as Ac_2O, trialkyl orthoformates, phthalic anhydride, and DCCI; or the use of Dean−Stark trap, sonication, and sealed tube failed to yield satisfactory results. However, the organocatalyst 1,1,3,3-tetramethylguanidine (TMG)[14] gave a yield of 30%. The stronger bases TBD, or Barton's, did not confer any advantage. Addition of TFAA for in situ conversion of the β-hydroxyl group into the TFA ester increased the yield to 40%. Excess TMG led to more side products, but DIEA as an auxiliary base (ineffective alone) increased the yield to 70%. The cis relationship between the C9−C14 and C12−C13 bonds (thermodynamic result) was confirmed by X-ray analysis (Figure 5, structure by X-ray).

Selective conjugate reduction of **7** to nitroalkane **8** (C9−C10 versus C5−C6) was accomplished with $NaCNBH_3$ in THF and pH 4 buffer in 70% yield. The stereochemical outcome is attributed to the nitronate intermediate being in equilibrium

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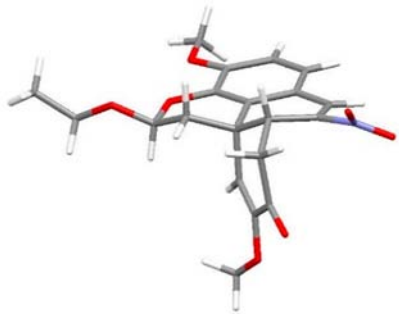

Figure 5. Nitroalkene (**7**) X-ray.

with the α-anion in which the lone pair occupies a pseudoaxial geometry where it is protonated. Furthermore, any pseudoaxial nitro group can epimerize to achieve the thermodynamic orientation. This was a necessary requirement as both the nitro group and the aldehyde must be on the same face of the molecule for subsequent annulation step post nitro reduction to form the D-ring (Figure 6, structure by X-ray).

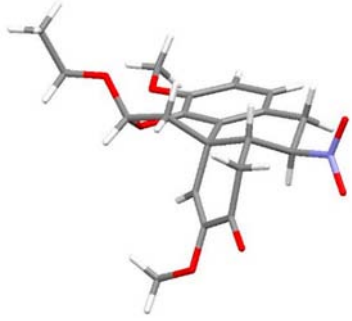

Figure 6. Nitroalkane (**8**) X-ray.

Selective reduction of the nitro group in **8** presented another major challenge. Conditions such as Zn,[15] Zn/HCO_2NH_4,[16] $Zn/H_2NNH_2.HCO_2H$,[17] In,[18] In/NH_4Cl,[19] Fe,[20] $Fe-FeCl_3$,[21] $Mg/H_2NNH_2{\cdot}HCO_2H$,[22] and $SnCl_2$, as well as Adam's and Lindlar's catalysts, either led to over-reduction or to no reaction. Transfer hydrogenation using HCO_2H or H_2 over 10% Pd/C led to over-reduction. On the other hand, use of HCO_2NH_4 with either 10% Pd/C[23] or RaNi returned the starting material. Remarkably, HCO_2H with catalytic RaNi[24] gave diastereomeric amine **9** in 88% yield (Figure 7, structure by X-ray).

Conversion of amine **9** into racemic core **10** (D-ring) was accomplished by an intramolecular reductive amination between C16 and the nitrogen via in situ hydrolysis of the acetal group using 0.5 N aqueous HCl at 100 °C followed by formation of an iminium ion and its reduction with $NaCNBH_3$ into a racemic mixture of amines **10** (8,14-dihydronorsalutaridine and norisosinomenine). No hydrolysis of the methyl enol ether occurred under these conditions. A yield of 70% was obtained for **10** which upon treatment with 37% $H_2CO_{(aq)}$, $NaCNBH_3$, and AcOH in EtOH[25] led to N-methylation to give **11** as a racemic mixture of isosinomenine and 8,14-dihydrosalutaridine in 91% yield (Figure 8, structure by X-ray).

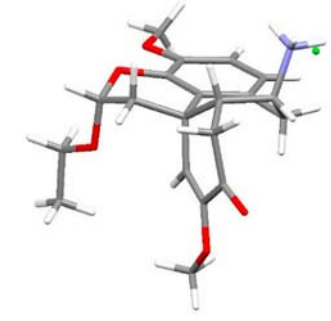

Figure 7. Amine (**9**) X-ray.

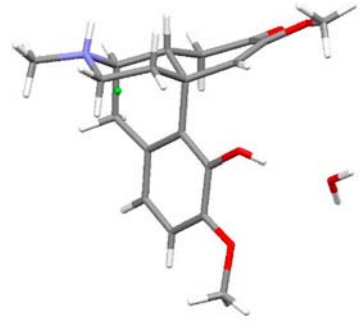

Figure 8. *N*-Methyl (**11**) X-ray.

The strategy presented here is an efficient (17% from **1**, 10 steps) racemic synthesis of the aforementioned 8,14-dihydromorphinandienone alkaloids. The synthesis furnishes the correct oxidation level of the target compounds by avoiding the biomimetic strategy of *o*,*p*-phenolic coupling. A unique route to a Henry–Michael–dehydration cascade has been developed where a variety of other conditions failed. The resultant aliphatic nitro group could be reduced selectively only under transfer hydrogenation conditions. The current strategy is complementary to that from our group for the synthesis of codeine[9] in that it begins with the C6 oxygen already in place, obviating the need for its later introduction over several steps. A one-step conversion of **7** to **9**, a one-pot conversion of **9** to **11**, and an asymmetrical conversion of **5** to **6** are topics for future consideration. Conversion of 8,14-dihydrosalutaridine into salutaridine (i.e., oxidation of C8–C14 into a double bond as exemplified by conversion of ocobotrine into sinoacutine via α-bromination-dehydrobromination[6a]) would allow for its subsequent transformation into thebaine[26] and codeine,[27] providing a practical synthesis of these iconic structures.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Texas at Austin, is thanked for the X-ray structure determination of intermediates **4**, **6a,b**, **7**−**9**, and **11**.

REFERENCES

(1) (a) Kutchan, T. M. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: London, 1998; Vol. *50*, p 257. (b) Barton, D. H. R.; Cohen, T. *Festschrift Arthur Stoll*; Birkhauser: Basel, 1957, 117. (c) Barton, D. H. R.; Kirby, G. W.; Steglich, W.; Thomas, G. M. *Proc. Chem. Soc.* **1963**, 203.

(2) (a) Haynes, L. J.; Stuart, K. L. *J. Chem. Soc.* **1963**, 1784. (b) Haynes, L. J.; Husbands, G. E. M.; Stuart, K. L. *J. Chem. Soc. C* **1968**, 951. (c) Haynes, L. J.; Husbands, G. E. M.; Stuart, K. L. *Chem. Commun.* **1967**, 15. (d) Stuart, K. L.; Woo-Ming, R. B. *Phytochemistry* **1969**, *8*, 777.

(3) (a) Reference 2c. (b) Reference 2d. (c) Reference 2b. (d) Mukhtar, M. R.; Hadi, A. H. A.; Litaudon, M.; Awang, K. *Fitoterapia* **2004**, *75*, 792. (e) Wei, Y.; Jin, Q. *Zhongguo Yaolixue Tongbao* **1997**, *13*, 180.

(4) (a) Sasaki, Y.; Ueda, S. *Yakugaku, Zasshi* **1958**, *78*, 44. (b) Sasaki, Y.; Ueda, S. *Yakugaku, Zasshi* **1963**, *83*, 418. (c) Barton, D. H. R.; Kirby, A. J.; Kirby, G. W. *J. Chem. Soc. (C)* **1968**, 929. (d) Okabe, K.; Kunio, H.; Sawa, Y. K. *Chem. Pharm. Bull.* **1968**, *16*, 1611.

(5) (a) Melo, P. S.; Cavalcante, H. M. M.; Barbosa-Filho, J. M.; Diniz, M. F. F. M.; de Medeiros, I. A.; Haun, M. *Toxicol. Lett.* **2003**, *142*, 143. (b) Cavalcante, H. M. M.; Riberio, T. P.; Silva, D. F.; Nunes, X. P.; Barbosa-Filho, J. M.; Diniz, M. F. F. M.; Correia, N. A.; Braga, V. A.; Medeiros, I. A. *Basic & Clinical Pharmacology & Toxicology* **2010**, *108*, 122. (c) Freitas, M. R.; Alencar, J. L.; Da-Cunha, E. V. L; Barbosa-Filho, J. M.; Gray, A. I. *Phytochemistry* **1995**, *40*, 1553. (d) ref 3-d.

(6) (a) Vecchietti, V.; Casagrande, C.; Ferrari, G. *Tetrahedron Lett.* **1976**, *19*, 1631. (b) Vecchietti, V.; Casagrande, C.; Ferrari, G.; Danieli, B.; Palmisano, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 578.

(7) (a) Ludwig, W.; Schafer, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1025. (b) Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. *J. Chem. Soc. C* **1969**, 2030. (c) Szantay, C.; Blasko, G.; Barczai-Beke, M.; Pechy, P.; Dornyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509. (d) Szantay, C.; Barczai-Beke, M.; Pechy, P.; Blasko, G.; Dornyei, G. *J. Org. Chem.* **1982**, *47*, 594. (e) Zenk, M. H.; Gerardy, R.; Stadler, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1725. (f) Wiegand, S.; Schafer, H. J. *Tetrahedron* **1995**, *51*, 5341. (g) Udvardy, A.; Sipos, A. *Cent. Eur. J. Chem.* **2013**, *11*, 2022.

(8) (a) Henry, L. C. R. *Acad. Sci. Ser. C* **1895**, 1265. (b) Henry, L. *Bull. Soc. Chim. Fr.* **1895**, *13*, 999. (c) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.

(9) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045.

(10) (a) Ono, N.*The Nitro Group in Organic Synthesis*; Wiley: New York, 2001. (b) Kabalka, G. W.; Varma, R. S. *Org. Prep. Proced. Int.* **1987**, *19*, 283. (c) Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487.

(11) (a) Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett.* **2004**, *45*, 2699. (b) Dandia, A.; Jain, A. K.; Sharma, S. *Tetrahedron Lett.* **2012**, *53*, 5859. (c) Yi, B.; Zhang, Y.; Zhang, R.; Dang, L.; Yang, H.; Qiu, M. *Adv. Sci. Lett.* **2012**, *10*, 375. (d) Greaves, T. L.; Drummond, C. J. *Chem. Rev.* **2008**, *108*, 206. (e) Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615.

(12) Ballini, R.; Bosica, G.; Forconi, P. *Tetrahedron* **1996**, *52*, 1677. (b) Ballini, R.; Bosica, G. *J. Org. Chem.* **1994**, *59*, 5466. (c) Ballini, R.; Barboni, L.; Palmieri, A. *Synlett.* **2007**, *19*, 3019. (d) Ballini, R.; Bosica, G.; Fiorin, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(13) (a) Vivek, J.; Bulbule, G. K.; Jnaneshwara, R. R. D.; Hanumant, B. B.; Vishnu, H. D. *Synth. Commun.* **2001**, *31*, 3623. (b) Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955. (c) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679.

(14) (a) *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; Wiley: New York, 2009. (b) Caubere, P. *Chem. Rev.* **1993**, *93*, 2317. (c) Gund, P. J. *J. Chem. Educ.* **1972**, *49*, 100. (d) Gobi, A.; Frenking, G. *J. Am. Chem. Soc.* **1993**, *115*, 2363. (e) Raczynska, E. D.; Cyranski, M. K.; Gutowski, M. *J. Phys. Org. Chem.* **2003**, *16*, 91.

(15) Leminger, O. *Chem. Prum.* **1972**, *22*, 553.

(16) Gowda, D.; Mahesh, B.; Shankare, G. *Ind. J. Chem. Sect. B* **2001**, *40*, 75.

(17) Gowda, S.; Gowda, B. K. K.; Gowda, D. C. *Synth. Commun.* **2003**, *33*, 281.

(18) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, *9*, 955.

(19) Banik, B. K.; Suhendra, M.; Banik, I.; Becker, F. F. *Synth. Commun.* **2000**, *30*, 3745.

(20) Gamble, A. B.; Garner, J.; Gordon, C. P.; O'Conner, S. M. J.; Keller, P. A. *Synth. Commun.* **2007**, *37*, 2777.

(21) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607.

(22) Abiraj, K.; Gowda, S.; Gowda, D. C. *Synth. React. Inorg. Met.-Org. Chem.* **2002**, *32*, 1409.

(23) (a) Ram, S.; Ehrenkanfer, R. E. *Tetrahedron Lett.* **1984**, *25*, 3415. (b) Kabalka, G. W.; Pace, R. D.; Wadgaonkar, P. P. *Synth. Commun.* **1990**, *20*, 2453.

(24) (a) Gowda, D. C.; Gowda, A. S. P.; Baba, A. R.; Gowda, S. *Synth. Commun.* **2000**, *30*, 2889. (b) Yuste, F.; Saldana, M.; Walls, F. *Tetrahedron Lett.* **1982**, *23*, 147.

(25) (a) Eschweiler, W. *Ber.* **1905**, *38*, 880. (b) Clark, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571. (c) Moore, M. L. *Org. React.* **1949**, *5*, 301. (d) Frakas, E.; Sunman, C. J. *J. Org. Chem.* **1985**, *50*, 1110.

(26) Barton, D. H. R.; Kirby, G. W.; Steglich, W.; Thomas, G. M.; Battersby, A. R.; Dobson, T. A.; Ramuz, H. *J. Chem. Soc.* **1965**, 2423.

(27) (a) Schopf, C.; Hirsch, H. *Annalen* **1913**, *489*, 224. (b) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109. (c) Barber, R. B.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1175.