Total Synthesis of Tropoloisoquinolines: Imerubrine, Isoimerubrine, and Grandirubrine[1]

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Abstract: A unified, ready access to the tropoloisoquinoline alkaloids imerubrine (**1**), grandirubrine (**2**), and isoimerubrine (**3**) is delineated and features sequential application of the intramolecular Diels−Alder reaction of an acetylene-tethered oxazole and the [4 + 3] cycloaddition of an oxyallyl. A regioselective synthesis of **1** was achieved by stereo- and regioselective oxidation of an 8-oxabicyclo[3.2.1]oct-6-en-3-one cycloadduct by means of the Moriarty method. Such a post-cycloaddition functionalization complements the synthetic utility of an α-alkoxy-substituted oxyallyl so as to broaden the scope of the oxyallyl [4 + 3] cycloaddition reaction.

Imerubrine (**1**), isolated from the plants *Abuta imene* and *Abuta refescens* of the *Menispermacae* family, was shown by X-ray analysis to possess an unusual tropolone ether structure (Figure 1).[2] Grandirubrine (**2**), the corresponding free tropolone, was subsequently isolated from *Abuta grandifolia*.[3] This unique class of naturally occurring tropoloisoquinoline alkaloids presently includes isoimerubrine (**3**), pareirubrines A and B (**4** and **5**), and pareitropone (**6**).[4] These alkaloids **1**−**6** are structurally similar to colchicine (**7**) and its congeners which are the only previously known tropoloisoquinoline alkaloids.[5] The biosynthetic pathways of their shared tropolone moieties were postulated to involve fused cyclopropane intermediates.[6] Such a biosynthesis might also account for the presence of the more widespread azafluoranthene alkaloids in the same *Abuta* plants.[2b] Cytotoxic properties were reported for some of these alkaloids, in particular **6**,[4] which might well be related to the well-known antimitotic properties of **7**. Both **4** and **5** were known to preferentially crystallize as the keto tautomers shown in Figure 1.

These alkaloids pose considerable synthetic challenges, which are in part due to the paucity of general methods for preparing the fused tropolone ring. To date, only two total syntheses of **1** and **2** were recorded: the Banwell group utilized an acid-promoted ring expansion of an appropriate homo-*o*-benzoquinone for the regioselective syntheses.[7] Boger's syntheses were based on the [4 + 2] cycloaddition reaction of a cyclopropenone ketal and an α-pyrone.[8] Another noteworthy thread of both of these elegant syntheses is characterized by the development of synthetic strategies which take advantage of the close structural relationship between these tropoloisoquinoline alkaloids and colchicine (**7**).[9] Herein we detail the regiocontrolled syntheses of **1**−**3** by extension of our previously reported synthesis of (−)-**7**,[10] which constitutes a unified entry to these structurally related alkaloids.

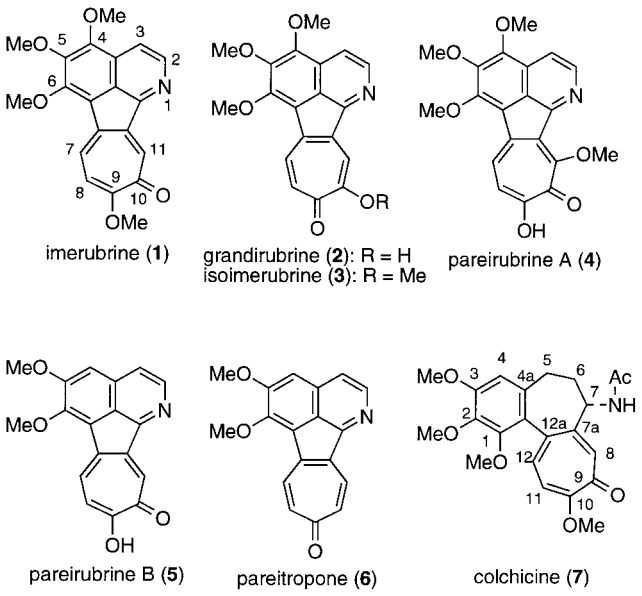

Figure 1.

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(1) Part 13 in the series of synthetic studies on [4 + 3] cycloadditions of oxyallyls. See also: (a) Part 12: Lee, J. C.; Cha, J. K. *Tetrahedron* **2000**, *56*, 10175. (b) Part 11: Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett*. **1999**, *1*, 2017.

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(5) For general reviews, see: (a) Buck, K. T. *Alkaloids (Academic Press)* **1984**, *23*, 301. (b) Wildman, W. C.; Pursey, B. A. *Alkaloids (Academic Press)* **1968**, *11*, 407. (c) Capraro, H.-G.; Brossi, A. *Alkaloids (Academic Press)* **1984**, *23*, 1. (d) Boyé, O.; Brossi, A. *Alkaloids (Academic Press)* **1992**, *41*, 125. (e) Le Hello, C. *Alkaloids (Academic Press)* **2000**, *53*, 287.

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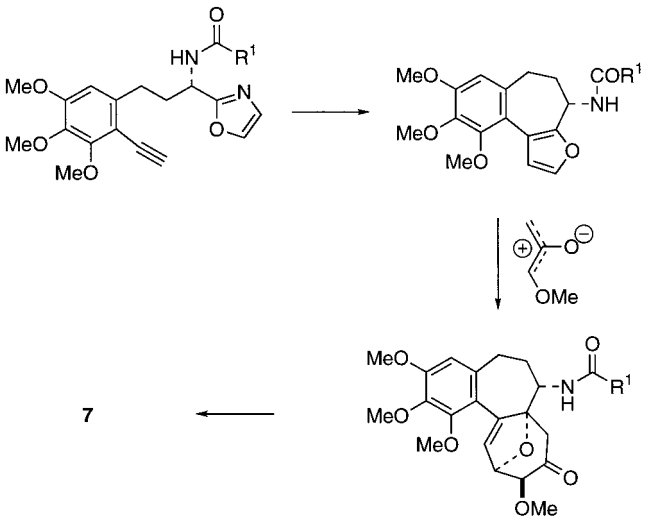
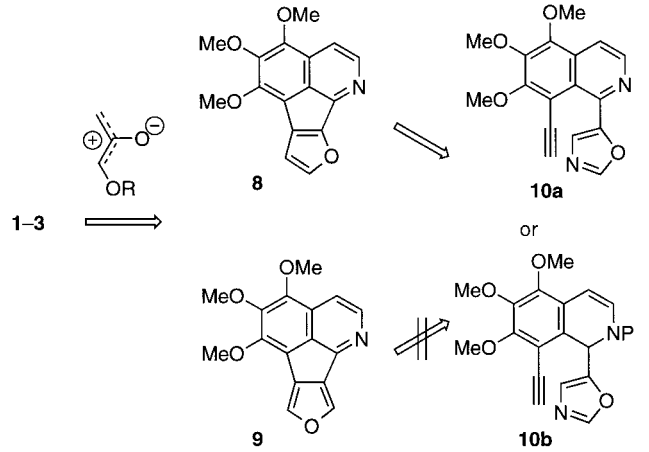
Scheme 1



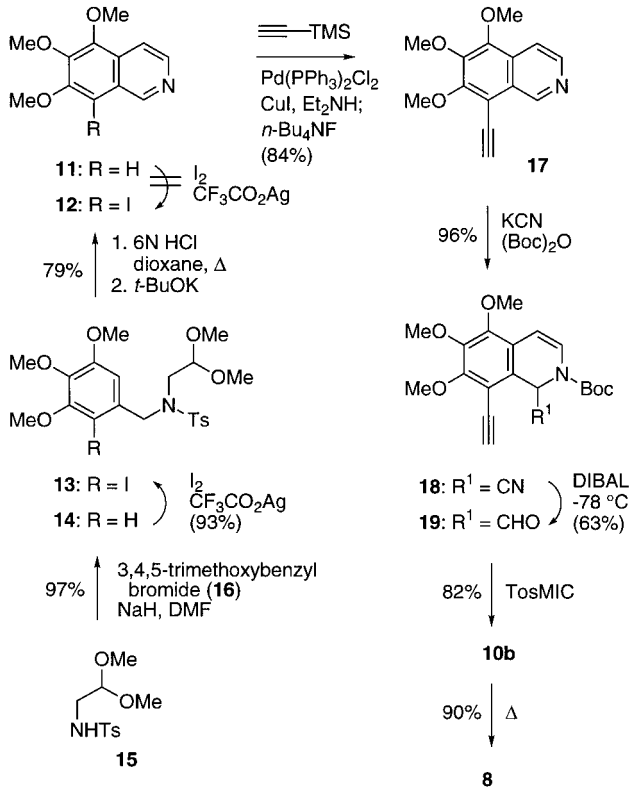
Scheme 2



Results and Discussion

Retrosynthetic Analysis. In parallel with the total synthesis of (−)-**7** (Scheme 1),[10] consecutive application of the intramolecular Diels−Alder reaction of an acetylene-tethered oxazole, the [4 + 3] cycloaddition of an oxyallyl, and double elimination of the resulting cycloadduct seemed to promise easy access to **1**−**3** and also other members of this family. The regiocontrolled introduction of the tropolone and tropolone ether subunits should be readily available by employing an α-alkoxy-substituted oxyallyl or the Moriarty oxidation of the unsubstituted [4 + 3] cycloadduct, as previously demonstrated in the preparation of simpler derivatives (e.g., hinokitiol).[11] Although both furans **8** and **9** could undergo the key oxyallyl cycloaddition reaction, **8** presented itself as an ideal advanced intermediate (Scheme 2): the regioselective introduction of the tropolone functionality was anticipated to be more facile than with the furan **9**; and the intramolecular Diels−Alder reaction of an acetylene-tethered oxazole **10** (as **10a** or **10b**) was also ideally suited for a convenient construction of the tetracyclic furan **8**, but not for **9**. Of particular interest was the investigation of the regiochemistry of the [4 + 3] cycloaddition of the highly functionalized furan **8** and an α-alkoxy oxyallyl in view of scant literature precedents. Finally, the preparation of **10** was in turn expected to be straightforward by means of the Sonogashira reaction and subsequent elaboration.

Scheme 3



Preparation of Furan 8. Our synthesis began with the known and readily available 5,6,7-trimethoxyisoquinoline (**11**).[12] The iodide **12** was required for the Sonogashira coupling with trimethylsilylacetylene.[13] Unfortunately, **11** proved to resist direct iodination, although acid-catalyzed bromination (NBS, H_2SO_4 catalyst) had successfully been achieved by Boger.[12] Thus, the iodo functionality was installed prior to the isoquinoline construction to afford **12** uneventfully by a slight modification of Boger's procedure (Scheme 3). Alkylation of *N*-*p*-toluenesulfonylaminoacetaldehyde dimethyl acetal (**15**) with 3,4,5-trimethoxybenzyl bromide (**16**), followed by iodination[14] of **14**, provided the aryl iodide **13** in 90% overall yield. Subsequent cyclization of **13** was best achieved in two steps to give **12** (75−80% yield) by treatment with 6 N HCl−dioxane, followed by base-induced elimination of *p*-toluenesulfonic acid (*t*-BuOK, room temperature). On the other hand, direct acid-mediated cyclization of **13** (in a 6 N HCl solution) resulted in **12** in only 10−30% yield, while the undesired 4-*p*-toluenesulfonylisoquinoline (structure not shown) was obtained in 60−70% yield. Acetylene **17** was then prepared in 84% overall yield by means of the Sonogashira reaction with trimethylsilylacetylene and subsequent removal of the silyl group by *n*-Bu_4NF.

The Reissert intermediate **18** was next prepared (96%) by employing $(Boc)_2O$−KCN to set the stage for the necessary introduction of the oxazole moiety to the isoquinoline **17**. DIBAL-H reduction of the cyano group of **18** to the aldehyde **19** proved to be challenging, probably due to steric congestion. Ultimately, **19** was obtained in 63% yield by employing an excess (2.5−5.0 equiv) of DIBAL-H at −78 °C in toluene. Treatment with TosMIC according to the procedure of van

(10) (a) Lee, J. C.; Jin, S.-j.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 2804. (b) Reference 1a.

(11) Lee, J. C.; Cho, S. Y.; Cha, J. K. *Tetrahedron Lett.* **1999**, *40*, 7675.

(12) (a) Boger, D. L.; Brotherton, C. E.; Kelley, M. D. *Tetrahedron* **1981**, *37*, 3977. (b) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.

(13) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Cf.: (b) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.

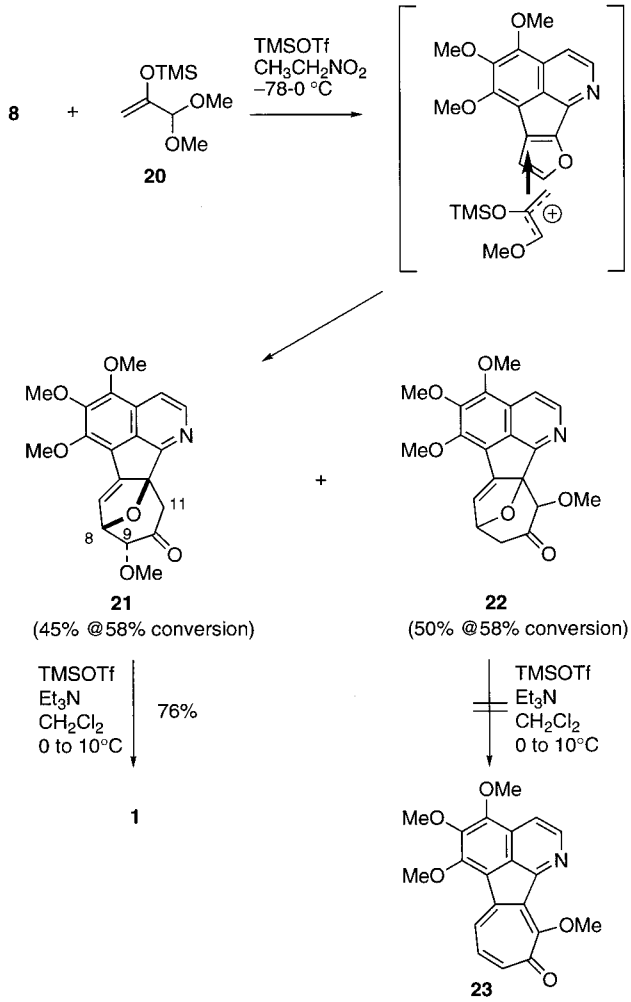
(14) Janssen, D. E.; Wilson, C. V. *Organic Synthesis*; Wiley: New York, 1963; Collect. Vol. IV, p 547.

Leusen[15] provided oxazole **10b** (where P = Boc) in 64% yield. The pivotal intramolecular Diels−Alder−retro-Diels−Alder reactions[16] of **10b** and concomitant elimination of the Boc group proceeded smoothly by thermolysis (*o*-dichlorobenzene, reflux) to furnish the requisite tetracyclic furan **8** in 85−90% yield.

Oxyallyl [4 + 3] Cycloaddition and Double Elimination. The key [4 + 3] cycloaddition reaction of **8** was achieved by adaptation of Albizati's procedure involving in situ generation (with TMSOTf) of the α-methoxy trimethylsiloxyallyl cation from the trimethylsilyl enol ether **20** of pyruvic aldehyde dimethyl acetal (Scheme 4).[17−19] Not surprisingly, a 1:1 mixture of the desired cycloadduct **21** (26%) and the regioisomer **22** (29%) were isolated, along with 42% of recovered starting material.[20] The overall yield and the material balance were optimal when the cycloaddition reaction was allowed to proceed to ∼50% conversion. Additionally, each cycloadduct proved to be a single diastereomer. The regiochemistry of these cycloadducts was unequivocally established from the splitting pattern (an AB quartet) of the methylene protons at C-11 or C-9 (imerubrine numbering). The stereochemistry of **21** was assigned on the basis of the diagnostic vicinal coupling constant (J = 5.0 Hz),[21] with which the exo proton at C-9 is coupled to the bridgehead proton at C-8. This stereochemical assignment was consistent with that of Albizati's previous examples involving simple furans[17] and can be rationalized by the "compact" (endo-like) transition state of the W-shaped oxyallyl cation as depicted in Scheme 4.[19] On the other hand, the stereochemistry of **22** could not be determined due to the absence of the vicinal coupling constant for the proton at C-11.

It is interesting to recall that the cognate cycloaddition reaction of the identical α-methoxy trimethylsiloxyallyl cation in the previous synthesis of (−)-colchicine took place with an exceptional level of regioselectivity,[10] where the regiodirecting influence of the C-3 aryl substituent of the furan substrate must outweigh that of the C-2 alkyl moiety. Thus, lack of regiocontrol in the cycloaddition of **8** can be attributed to the presence of the two aryl groups at C-2 and C-3 of the furan functionality, which are anticipated to exert comparable directing power.

Scheme 4



Finally, as demonstrated in the previous synthesis of (−)-colchicine, treatment of **21** with excess amounts of TMSOTf and Et_3N in CH_2Cl_2 by a slight modification of the Föhlisch and Mann methods[22] gave imerubrine (**1**) in 76% yield. The synthetic substance was found to exhibit identical physical and spectroscopic data to those reported for the natural product, as well as the synthetic material.[2,7,8] In contrast, **22** proved resistant toward elimination of the ether bridge under identical conditions. While speculative at this juncture, it is tempting to suggest that the unexpected failure of **22** to undergo ring opening might be attributed to the axial orientation of the methoxy group at C-11, which should impede the requisite enolization, an obligatory step for double elimination of the oxa bridge.

Regioselective Synthesis of 1. To improve on the nonregioselective cycloaddition reaction of **8** and α-methoxy oxyallyl, a regiocontrolled synthesis of **1** would seem attainable by elaboration of the unsubstituted [4 + 3] cycloadduct. The Moriarty oxidation[23] of 8-oxabicyclo[3.2.1]oct-6-en-3-one compounds was previously shown to be very sensitive to steric effects, and the desired regioisomer was thus anticipated to be the major, if not the sole, product (vide infra).[11] Toward this

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(16) An efficient assembly of fused-ring furans from acetylene-tethered oxazoles has been amply demonstrated by Jacobi and co-workers: Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc*. **1991**, *113*, 5384 and references therein.

(17) Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109.

(18) Until recently the preparation of α-heteroatom-substituted oxyallyl cations has received relatively scant attention: (a) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693. (b) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Käshammer, D. *Chem. Ber*. **1988**, *121*, 1585. (c) Reference 17. (d) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1266. See also: (e) Harmata, M.; Jones, D. E. *Tetrahedron Lett*. **1997**, *38*, 3861. (f) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett*. **1999**, *40*, 1831. See also: (g) Harmata, M.; Fletcher, V. R.; Claassen, R. J., II *J. Am. Chem. Soc*. **1991**, *113*, 9861. (h) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett*. **1995**, *36*, 23. (i) Walters, M. A.; Arcand, H. R. *J. Org. Chem*. **1996**, *61*, 1478. For a recent review on this important area, see: (j) Harmata, M. *Recent Res. Dev. Org. Chem*. **1997**, *1*, 523.

(19) For general reviews of the oxyallyl [4 + 3] cycloadditons, see: (a) Noyori, R.; Hayakawa, Y. *Org. React*. **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Rigby, J. H.; Pigge, F. C. *Org. React*. **1997**, *51*, 351.

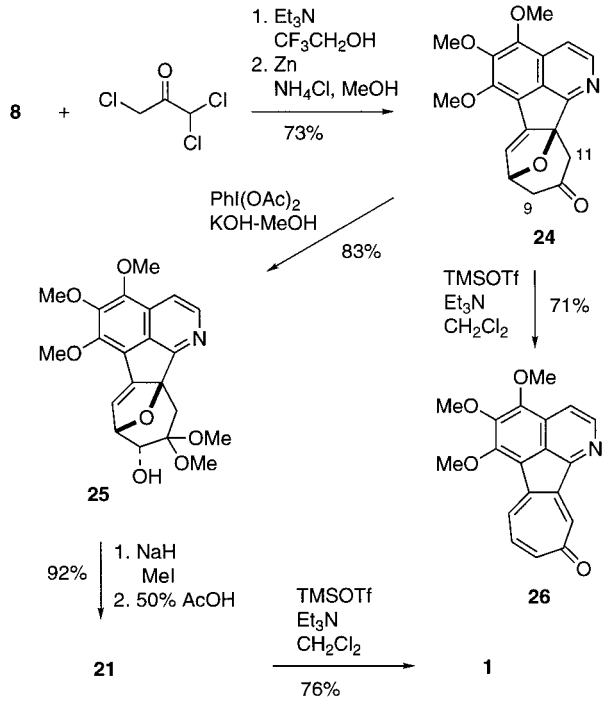
(20) The regiochemistry of the oxyallyl cycloaddition in the synthesis of colchine (**7**) is controlled by the C-3 aryl moiety of the furan in preference to the C-2 alkyl group (Scheme 1). In contrast, the two aryl groups at C-2 and C-3 in the cycloaddition reaction of **8** are expected to exert comparable directing effects in opposition to each other. In the synthesis of **7**, there was also an unusual directing influence by the amino protecting group.

(21) (a) Hoffmann, H. M. R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc*. **1972**, *94*, 3940. (b) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc*. **1978**, *100*, 1765.

(22) (a) Föhlisch, B.; Sendelbach, S.; Bauer, H. *Liebigs Ann. Chem*. **1987**, 1. (b) Barbosa, L.-C. A.; Mann, J.; Wilde, P. D. *Tetrahedron* **1989**, *45*, 4619. (c) For an excellent review on ring-opening reactions of oxabicylic compounds, see: Chiu, P.; Lautens, M. *Top. Curr. Chem*. **1997**, *190*, 1.

(23) (a) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett*. **1981**, *22*, 1283. (b) Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R.; Vaid, R. K.; Freeman, W. A. *J. Org. Chem*. **1989**, *54*, 4008. (c) Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett*. **1992**, *33*, 6065.

Scheme 5



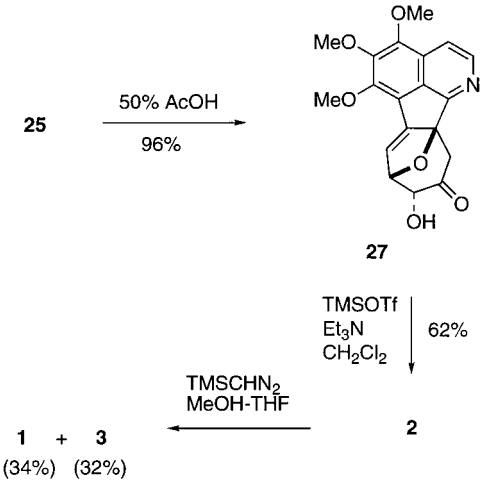
end, the [4 + 3] cycloadduct **24** was first secured in 73% overall yield by way of the Föhlisch reaction[24] (Scheme 5). It was pleasing that the Moriarty oxidation [i.e., treatment with (diacetoxyiodo)benzene in methanolic potassium hydroxide] of ketone **24** indeed gave **25** as the sole regioisomer in 83% yield. In passing, we note that the stereochemical outcome of the Moriarty oxidation of 8-oxabicyclo[3.2.1]oct-6-en-3-ones complements that of the Rubottom-type oxidation of the corresponding silyl enol ether or of the related direct hydroxylation of the enolate.[25] In any event, **25** was uneventfully converted (92%) by *O*-methylation and subsequent acidic hydrolysis to the α-methoxyketone **21**, which was identical in all aspects to that which was previously prepared by means of an α-methoxy oxyallyl (Scheme 4). Thus, the sequential application of the Föhlisch cycloaddition, the Moriarty oxidation, and ring opening afforded a regioselective synthesis of **1**.

Total Synthesis of 2 and 3. Double elimination of **24** under typical conditions gave granditropone (**26**), which had previously been prepared by Boger[8] to serve as the key precursor to **1**−**3**.

(24) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Henle, G. H.; Korfant, H.; Reiner, S.; Föhlisch, B. *J. Org. Chem.* **1999**, *64*, 3398 and references therein.

(25) For related chemistry, see also: (a) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207. (b) Gethin, D. M.; Simpkins, N. S. *Tetrahedron* **1997**, *53*, 14417.

Scheme 6



A convenient synthesis of grandirubrine (**2**) was directly available (62%) by ring opening of the α-hydroxy ketone **27**, which was in turn prepared (96%) by acidic hydrolysis of **25** with no evidence of potential tautomerization (Scheme 6). Finally, as previously reported by Cava, Itokawa, and Boger,[3,4d,8] treatment of **2** with $TMSCHN_2$ resulted in a 1:1 mixture of **1** and **3**. The synthetic substances **1**−**3** were shown to exhibit the identical physical and spectroscopic data to those reported for the natural products, as well as the synthetic materials.[2,7,8]

Conclusion

The [4 + 3] cycloaddition reaction of an oxyallyl to a suitably functionalized furan, followed by double elimination of the resulting oxa bridge, has provided ready access to the tropoloisoquinoline alkaloids, imerubrine, grandirubrine, and isoimerubrine (**1**−**3**), as well as colchicine (**7**). The requisite furan substrate was readily prepared by the intramolecular Diels−Alder reaction of an acetylene-tethered oxazole. Additionally, stereo- and regioselective oxidation of the 8-oxabicyclo[3.2.1]-oct-6-en-3-one cycloadducts by means of the Moriarty method provided a regioselective synthesis of **1** and broadened the scope of the oxyallyl [4 + 3] cycloaddition.

Acknowledgment. This work is dedicated to the memory of Professor Arthur G. Schultz. We thank the National Institutes of Health for generous financial support (GM35956).

Supporting Information Available: Experimental procedure and the ^1H and ^{13}C NMR spectra of all synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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