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Syntheses of Ficuseptine, Juliprosine, and Juliprosopine by Biomimetic Intramolecular Chichibabin Pyridine Syntheses

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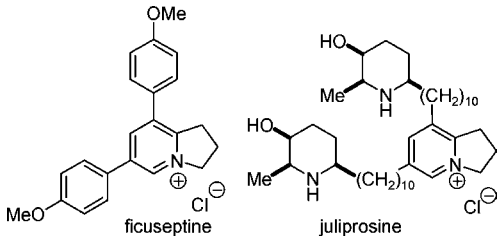
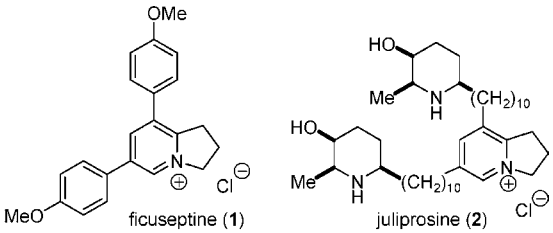
ABSTRACT



Biomimetic intramolecular Chichibabin pyridine syntheses using two molecules of an aldehyde and 4-aminobutanal dimethyl acetal (6) proceed efficiently in AcOH at 95 °C to give 2,3-dihydro-1*H*-indolizinium salts. Reaction occurs at 25 °C if 1-pyrroline (5) is used instead of 6. This reaction has been used for a one-step synthesis of ficuseptine (1) and the first syntheses of juliprosine (2) and juliprosopine (17t), which is now assigned as the trans stereoisomer.

The 2,3-dihydro-1*H*-indolizinium alkaloid ficuseptine (**1**) with significant antibacterial and antifungal activity was isolated from the leaves of *Ficus septica*.[1] Juliprosine (**2**) with an identical core was isolated from *Prosopis juliflora* by Hesse and co-workers.[2] Related alkaloids varying in the stereochemistry of the piperidine moieties or the oxidation state of the piperidine or indolizinium core are also known.[3,4] Bracher and Daab recently reported a five-step synthesis of ficuseptine (**1**) using Suzuki and Sonogashira couplings and a Sandmeyer iodination.[5] Although syntheses of monomeric piperidine alkaloids related to juliprosine (**2**) have been extensively investigated,[6] the preparation of the 2,3-dihydro-1*H*-indolizinium core has not been addressed.



We thought that the 2,3-dihydro-1*H*-indolizinium core of **1** and **2** might be formed in a single biomimetic step by an intramolecular Chichibabin pyridine synthesis from two molecules of aldehyde **4** and one molecule of either 1-pyr-

(1) Baumgartner, B.; Erdelmeier, C. A. J.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3327−3330.

(2) Dätwyler, P.; Ott-Longoni, R.; Schöpp, E.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 1959−1963.

(3) (a) Ott-Longoni, R.; Viswanathan, N.; Hesse, M. *Helv. Chim. Acta* **1980**, *63*, 2119−2129. (b) Ahmad, V. U.; Sultana, A.; Qazi, S. *J. Nat. Prod.* **1989**, *52*, 497−501. (c) Astudillo, L.; Jürgens, K.; Schmeda-Hirschmann, G.; Griffith, G. A.; Holt, D. J.; Jenkins, P. R. *Planta Med.* **1999**, *65*, 161−162. (d) Nakano, H.; Nakajima, E.; Hiradate, S.; Fujii, Y.; Yamada, K.; Shigemori, H.; Hasegawa, K. *Phytochemistry* **2004**, *65*, 587−591.

(4) Michael, J. P. In *Alkaloids, Chemistry and Biology*; Cordell, G. A., Eds.; Academic Press: San Diego, 2001; Vol. 55, pp 91−258.

(5) Bracher, F.; Daab, J. *Eur. J. Org. Chem.* **2002**, 2288−2291.

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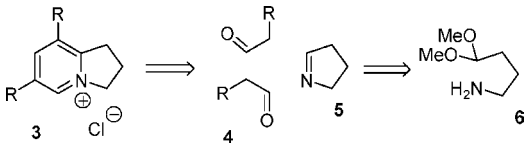
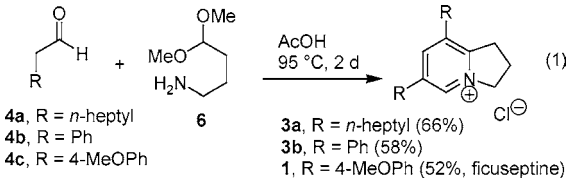
roline (**5**)[7] or 4-aminobutanal dimethyl acetal (**6**), which is readily available and has been widely used in biomimetic alkaloid syntheses (see Scheme 1).[8] The Chichibabin formation of pyridinium salts by the condensation of three molecules of an aldehyde and a primary amine and oxidation of the resulting dihydropyridine has been extensively studied[9,10] and occurs readily in AcOH at or slightly above room temperature.[10c] To the best of our knowledge, the intramolecular variant, in which the amine and one of the aldehydes are connected by a tether, has not been reported.

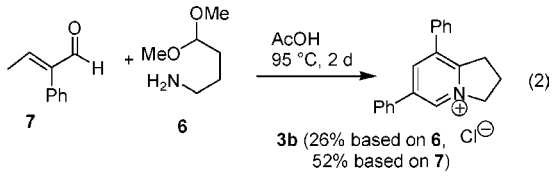
Scheme 1. Retrosynthesis of 2,3-Dihydro-1*H*-indolizinium Salts



We were delighted to find that reaction of 2 equiv of nonanal (**4a**) with 4-aminobutanal dimethyl acetal (**6**) in AcOH at 95 °C for 2 d afforded 66% of the desired 2,3-dihydro-1*H*-indolizinium salt **3a** (see eq 1). Similar reactions with phenylacetaldehyde (**4b**) and 4-methoxyphenylacetaldehyde (**4c**) provided **3b** (58%) and **1** (ficuseptine, 52%), respectively.[11] This biomimetic approach provides facile access to ficuseptine (**1**) and other novel 2,3-dihydro-1*H*-indolizinium salts in only a single step.

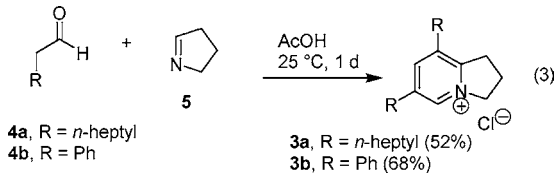


Surprisingly, reaction of 1 equiv of 2-phenyl-2-butenal (**7**) with **6** in AcOH at 95 °C also gave **3b** in 26% yield based on **6** or 52% yield based on the derived aldehyde **4b** (see eq 2). The formation of **3b** from **7** indicates that a retro-aldol reaction[12] occurred under these conditions to give phenylacetaldehyde (**4b**) and volatile acetaldehyde. This suggests that an enal formed by an aldol reaction of two molecules of an aldehyde might not be an intermediate in the Chichibabin reaction. This was confirmed by reaction of the aldol dimer of **4a**, 2-heptyl-2-undecenal, with **6** in AcOH at 95 °C, which proceeded much more slowly than with 2 equiv of **4a** and gave only a low yield of **3a**.



Although the successful formation of **3** in 52−66% yield in a single step was very satisfying, we were somewhat concerned about the high temperature required for this reaction, which might not be compatible with a sensitive aldehyde. Monitoring the reaction of nonanal (**4a**) with **6** in CD_3CO_2D at lower temperatures indicated that aldol dimerization of **4a** and dehydration to form 2-heptyl-2-undecenal occurred readily suggesting that the hydrolysis of the dimethyl acetal of **6** might be the slow step that necessitated the use of elevated temperatures. Struve and Christophersen recently reported a procedure to hydrolyze **6** to cleanly form 1-pyrroline (**5**) with aqueous hydrochloric acid.[7] If hydrolysis of the acetal of **6** is the slow step in the formation of **3**, reaction of **5** and **4** should proceed to give **3** under milder conditions.

As we had hoped, reaction of **5** with **4a** or **4b** in AcOH at 25 °C for 1 d gave the 2,3-dihydro-1*H*-indolizinium cations **3a** and **3b** in 52% and 68% yield, respectively (see eq 3). Thus, the Chichibabin pyridine synthesis using **5** proceeds under very mild conditions that should be compatible with sensitive aldehydes.



We now turned our attention to the preparation of aldehyde precursor **15** of juliprosine (**2**). The preparation of all-cis 6-alkyl-2-methyl-3-piperidinols has been extensively developed because several natural products have this skeleton with varying oxygen functionality at the terminus of the alkyl chain.[6] Since our interest was the formation of the 2,3-dihydro-1*H*-indolizinium dimer, we decided to adapt the very short route of Hasseberg and Gerlach, which provides facile access to **15** in quantity,[13] albeit in racemic form. Dimerization of racemic **15** will, of course, give juliprosine (**2**) as a mixture of racemic diastereomers. However, since

(6) For leading references from 2002 to 2004, see: (a) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711−7715. (b) Sato, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3839−3842. (c) Ma, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963−3965. (d) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001−6009. (e) Randl, S.; Blechert, S. *Tetrahedron Lett.* **2004**, *45*, 1167−1169. (f) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029−4031.

(7) Struve, C.; Christophersen, C. *Heterocycles* **2003**, *60*, 1907−1914.

(8) (a) King, F. D. *Tetrahedron Lett.* **1983**, *24*, 3281−3282. (b) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685−690. (c) Gribble, G. W.; Switzer, F. L.; Soll, R. M. *J. Org. Chem.* **1988**, *53*, 3164−3170.

(9) For reviews, see: (a) Gelas, J. *Bull. Soc. Chim. Fr.* **1967**, 3093−3101. (b) Sagitullin, R. S.; Shkil, G. P.; Nosonova, I. I.; Ferber, A. A. *Khim. Geterotsikl. Soedi.* **1996**, *2*, 147−161; *Chem. Abstr.* **1996**, *125*, 195291a.

(10) (a) Patrick, T. M., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2984−2986. (b) Farley, C. P.; Eliel, E. L. *J. Am. Chem. Soc.* **1956**, *78*, 3477−3484. (c) Charman, H. B.; Rowe, J. M. *Chem. Commun.* **1971**, 476−477. (d) Suyama, K.; Adachi, S. *J. Org. Chem.* **1979**, *44*, 1417−1420. (e) Yu, L.-B.; Chen, D.; Li, J.; Ramirez, J.; Wang, P. G.; Bott, S. G. *J. Org. Chem.* **1997**, *62*, 208−211.

(11) The spectral data of **1** are identical to those previously reported.[1,5]

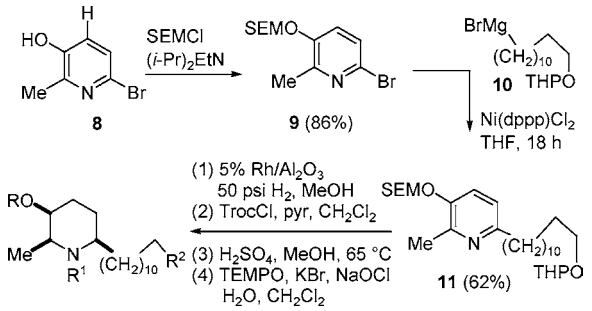
(12) Josephson, D. B.; Lindsay, R. C. *J. Am. Oil Chem. Soc.* **1987**, *64*, 132−138.

(13) Hasseberg, H.-A.; Gerlach, H. *Liebigs Ann. Chem.* **1989**, 255−261.

the stereocenters are separated by more than 20 atoms, this will have no effect on the spectral or chromatographic properties and will allow us to easily determine whether the piperidinol is compatible with the intramolecular Chichibabin pyridine synthesis.

Protection of bromopyridinol **8**[14] with SEMCl afforded 86% of **9**[13] (see Scheme 2). Kumada coupling of **9** with

Scheme 2. Synthesis of Aldehyde **15**



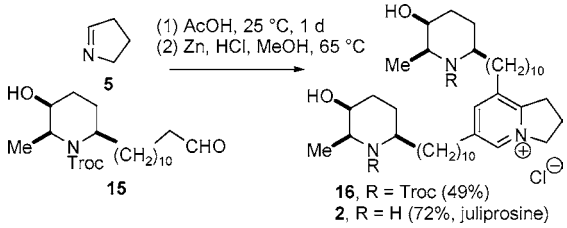
12, R = SEM, R^1 = H, R^2 = CH_2OTHP (90%)
13, R = SEM, R^1 = Troc, R^2 = CH_2OTHP (97%)
14, R = H, R^1 = Troc, R^2 = CH_2OH (97%)
15, R = H, R^1 = Troc, R^2 = CHO (72%, 88% BRSM)

Grignard reagent **10**[15] afforded 62% of **11**. Hydrogenation of **11** over 5% Rh/Al_2O_3 in MeOH as described by Hasseberg and Gerlach gave 90% of **12** with all-cis stereochemistry. Protection of the piperidine with TrocCl afforded 97% of **13**, which was hydrolyzed with sulfuric acid in MeOH to give 97% of diol **14**. Selective oxidation of the primary alcohol with TEMPO, KBr, and NaOCl[16] gave 72% (88% based on recovered **14**) of the required aldehyde **15**.[17]

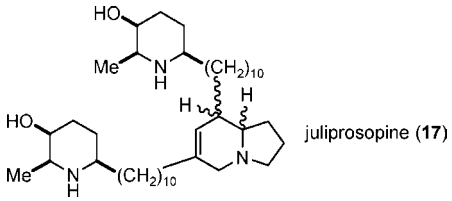
Condensation of 2 equiv of **15** with **5** in AcOH at 25 °C for 1 d provided 49% of the bis-Troc derivative of juliprosine (**16**)[18] (see Scheme 3). Condensation of **15** with acetal **6** at 95 °C was much less successful, affording only 18% of **16**. This clearly indicates the value of the two-step sequence with prior hydrolysis of the acetal of **6** with sensitive and expensive aldehydes. Deprotection of **16** with Zn dust in MeOH/HCl at reflux gave 72% of juliprosine (**2**),[18] with spectral data identical to those previously reported.[2] The ^1H and ^{13}C NMR spectral data of the bis hydrochloride salt of **2** are identical to those of an authentic sample kindly provided by Prof. Hesse.

The relative stereochemistry of the hexahydroindolizine ring of juliprosopine (**17**), another member of this family

Scheme 3. Synthesis of Juliprosine (**2**)

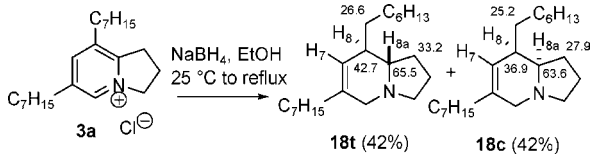


first isolated 25 years ago,[3a] had not been established. We thought that the synthesis of **17** might be achieved by reduction of juliprosine (**2**) and decided to explore this reaction initially with model **3a**.



Reduction[19] of **3a** with $NaBH_4$ in EtOH at 25 °C for 30 min and reflux for 30 min afforded 84% of a readily separable 1:1 mixture of hexahydroindolizine **18t** and **18c** (see Scheme 4). The regio- and stereochemistry of the two

Scheme 4. Reduction of **3a**



isomers of **18** were easily established by careful analysis of the spectral data since both stereoisomers are available. Both isomers show an AB pattern for the isolated allylic CH_2N group indicating that they are stereoisomers, not double-bond position isomers. Both isomers show Bohlmann bands[20] at 2850 and 2780 cm^{-1}, indicating that they exist in conformations with the nitrogen lone pair anti to the ring fusion hydrogen as calculated by MMX.[21] The coupling constant between H_7 and H_8 is <2 Hz in **18t** and 4.3 Hz in **18c**. MMX[21] calculated values are 2.7 Hz (79°) and 4.9 Hz (41°),

(14) Meana, Á.; Rodríguez, J. F.; Sanz-Tejedor, M. A.; García-Ruano, J. L. *Synlett* **2003**, *11*, 1678−1682.

(15) (a) Baldwin, J. E.; Spring, D. R.; Atkinson, C. E.; Lee, V. *Tetrahedron* **1998**, *54*, 13655−13680. (b) Pomerantz, M.; Liu, L.; Zhang, X. *ARKIVOC* **2003**, Part xii, 119−137; http://www.arkat-usa.org/ark/journal/2003/I12_Shine/HS-830J/HS-830J.pdf; *Chem. Abstr.* **2004**, *141*, 55000k.

(16) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562.

(17) Hydrolysis of **11** with sulfuric acid in MeOH at reflux followed by hydrogenation over 5% Rh/Al_2O_3 afforded the natural product (2α,5α,6α)-5-hydroxy-6-methyl-2-piperidinedodecanol.[3c]

(18) Compounds **16** and **2** are mixtures of two diastereomers because **15** is racemic, although only a single enantiomer is drawn. Similarly, compounds **17c, 17t**, **24c**, and **24t** are mixtures of four diastereomers. Only the relative stereochemistry within each of the three ring systems is specified.

(19) (a) Lyle, R. E.; Anderson, R. S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1966; Vol. 6, pp 45−93. (b) Ferles, M.; Pliml, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1970; Vol. 12, pp 43−101. (c) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082−12089.

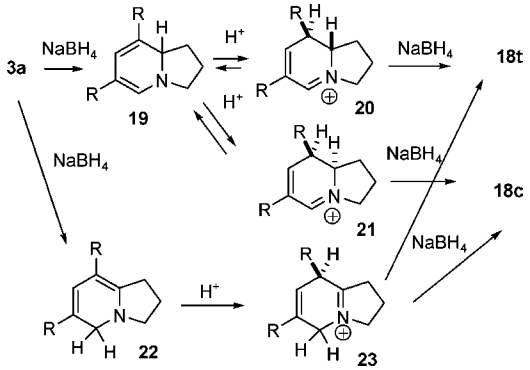
(20) (a) Rader, C. P.; Young, R. L., Jr.; Aaron, H. S. *J. Org. Chem.* **1965**, *30*, 1536−1539. (b) Aaron, H. S.; Ferguson, C. P. *Tetrahedron Lett.* **1968**, 6191−6194. (c) Ringdahl, B.; Pinder, A. R.; Pereira, W. E., Jr.; Oppenheimer, N. J.; Craig, J. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1−4. (d) Fleurant, A.; Saliou, C.; Célérier, J. P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, *32*, 255−258.

(21) PCMODEL version 8.0 from Serena Software was used.

respectively. Most significantly, the ^{13}C NMR shifts of C_1, C_{8a}, C_8, and C_8CH_2 are shifted upfield from 33.2, 65.5, 42.7, and 26.6 in **18t** to 27.9, 63.6, 36.9, and 25.2 in **18c** by gauche interactions in the cis isomer.[22] As expected,[20c] H_{8a} absorbs between δ 1−2 in both isomers of **18** so that coupling constants to this proton cannot be determined. However, H_{8a} in the hydrochloride salt of **18t** absorbs at δ 3.08 (ddd, 1, J = 11.0, 11.0, 7.3 Hz) in CD_3OD. The 11.0 Hz coupling constant between H_8 and H_{8a} indicates that these hydrogens are close to anti-periplanar, confirming the assignment of trans stereochemistry. The spectral data of **18t** correspond closely with those of the core of juliprosopine (**17**) so the natural product can now be assigned as the trans isomer **17t**.

The origin of the stereochemistry in the reduction of **3a** is not clear. The reduction could occur by addition of hydride to the ring fusion to give dihydropyridine **19** (see Scheme 5). Protonation, possibly reversible, would give a mixture

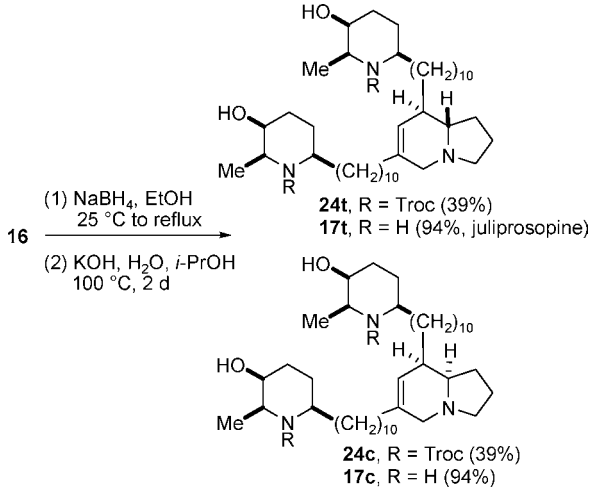
Scheme 5



of cations **20** and **21**, which will be reduced to **18t** and **18c**, respectively. The reduction could also occur to give dihydropyridine **22**. Protonation would give cation **23**, which would be expected to be reduced mainly from the less hindered bottom face to give predominantly the cis isomer **18c**.[23]

Reduction of juliprosine (**2**) with $NaBH_4$ in EtOH afforded an intractable mixture of **17t** and **17c**. Fortunately, reduction of bis-Troc-protected juliprosine (**16**) with $NaBH_4$ in EtOH for 30 min at 25 °C and 30 min at reflux provided a readily separable 1:1 mixture of **24t** (39%) and **24c** (39%)[18] (see Scheme 6). Reductive deprotection of **24** with Zn was

Scheme 6. Synthesis of Juliprosopine (**17t**)



problematic; considerable amounts of dichloroethyl carbamates were formed.[24] Cleavage of the Troc groups of **24t** by Overman's procedure[25] with KOH in aqueous 2-propanol in a sealed tube at 100 °C for 2 d afforded juliprosopine (**17t**)[18] in 94% yield with spectral data identical to those reported.[3a] The analogous deprotection of **24c**[18] afforded **17c** in 94% yield.

In conclusion, we have developed a very efficient intramolecular variant of the Chichibabin pyridine synthesis starting with 1-pyrroline (**5**) or amino acetal **6** and 2 equiv of an aldehyde that leads to 2,3-dihydro-1*H*-indolizinium alkaloid ficuseptine (**1**) in one step. We have used this reaction as the key step in the first syntheses of juliprosine (**2**) and juliprosopine (**17t**), whose stereochemistry has now been assigned as trans.

Acknowledgment. We thank the NIH (GM50151) for generous financial support. We thank Prof. Manfred Hesse for a sample of juliprosine (**2**). B.J.N. thanks Procter & Gamble Pharmaceuticals for a research fellowship.

Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) In *trans*-octahydro-8-methylindolizine, the ^{13}C NMR shifts of C_{8a}, C_8, and C_8Me are 73.5, 33.5, and 18.4. These carbons are shifted upfield to 65.9, 29.5, and 18.3 in the cis isomer by gauche interactions: Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Vennall, G. P. *Chem.—Eur. J.* **2002**, *8*, 195−207.

(23) (a) Hanaoka, M.; Yoshida, S.; Mukai, C. *Chem. Pharm. Bull.* **1989**, *37*, 3264−3267. (b) Tietze, L. F.; Brill, G. *Liebigs Ann. Chem.* **1987**, 311−319. (c) Hanaoka, M.; Hirasawa, T.; Cho, W. J.; Yasuda, S. *Chem. Pharm. Bull.* **2000**, *48*, 399−404.

(24) (a) Henkel, J. G.; Faith, W. C. *J. Org. Chem.* **1981**, *46*, 4953−4959. (b) Khanjin, N. A.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 2028−2057.

(25) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373−5379.