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An Access to the Bicyclic Nucleus of the Sponge Alkaloid Halicyclamine A by Successive Condensation of Malondialdehyde Units, Aldehyde Derivatives, and Primary Amines

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First results of an evaluation of the synthetic sequence depicted in Scheme 4 are reported. This sequence is based upon biosynthetic considerations concerning the manzamine family of sponge alkaloids. Stable equivalents **21** and **31** of the tetraaldehyde **7** have thus been obtained by using the chemistry of malondialdehyde previously reported by Tietze. These compounds afforded pyridinium salts **23** and **33** when treated with a primary amine in acidic medium. Further reductive amination and cyclization yielded bicyclic derivatives **25** and **35**, thus demonstrating the feasibility of this synthetic approach for the preparation of halicyclamine derivatives **13**. Products resulting from cycloaddition reactions leading to **9** were not observed.

Introduction

Numerous new alkaloids have been recently isolated from sponges of the order *Haplosclerida*.[1] The most well-known natural product in this series is probably manzamine A (Scheme 1) owing to its original structure and biological activity.[2]

The intriguing problem of the biosynthetic origin of manzamine A can be rather well rationalized starting from a comparison with a natural analogue, manzamine C (Scheme 1). Indeed, both products can be formed by reductive condensation of tryptamine with strictly identical precursors: a three-carbon unit (for example, malondialdehyde **1**), a dialdehyde **2** derived from fatty acids, and ammonia. Considering this hypothesis, the only difference in origin between these alkaloids would be that manzamine C is formed from one molecule of each precursor and tryptamine, while manzamine A is the result of condensation of two molecules of the same precursors **1** and **2** and tryptamine.

Such an hypothesis was initially formulated by Baldwin and Whitehead and experimentally investigated.[3] In this proposal involving dihydropyridine and dihydropyridinium salt intermediates, acrolein was proposed as the three-carbon unit. We suggested later that involvement of malondialdehyde **1** instead of acrolein would have some advantages since it can also explain the biosynthesis of natural pyridinium salts according to Scheme 2.[4] Experimental results supported rather well this modified hypothesis, in particular with respect to the synthesis of the ABC ring of manzamine A.[5]

While these models thus gave encouraging synthetic results, they all implicated intermediate dihydropyridium salts, as initially postulated by Baldwin and Whitehead. Accordingly, fundamental studies concerning the condensation of molecules such as **1** and **2** or their equivalents remained to be performed. For these reasons we recently embarked on model experiments addressing the problem of the multicomponent condensation depicted in Scheme 1 and summarized in Scheme 3.

Such condensations were expected to be of potential synthetic value for the generation of a variety of natural (or eventually nonnatural) molecular scaffolds. Thus, for example (Scheme 4), this process can produce the tetraaldehyde intermediate **7**. Reaction of this intermediate with primary amines (adducts **8** and **11**) can lead, via formation of a new carbon−carbon bond (**8** → **9**), to the manzamine A skeleton **10** or, via the formation of a pyridinium salt **12**, to the natural halicyclamine A[6] skeleton **13**.

In this paper we report a synthesis of stable equivalents of tetraaldehyde **7** and their transformation into the bicyclic skeleton of halicyclamine A according to a process similar to the sequence **7** → **13**.

Results and Discussion

There are many different ways of assembling aldehydes **1**, **3**, and **4** and amine precursors **5** and **6** shown

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(4) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026−8034.

(5) (a) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890−1897. (b) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Almourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381−7387.

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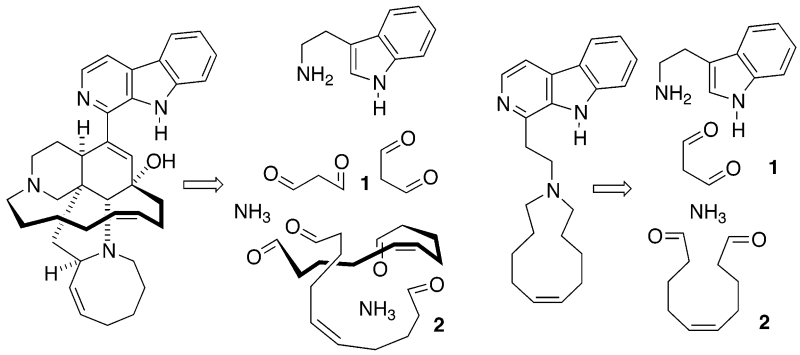
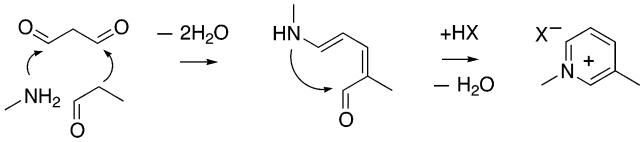
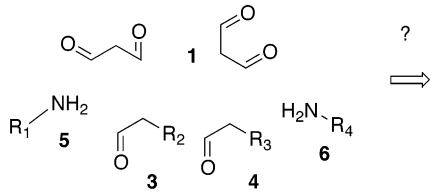
SCHEME 1



SCHEME 2



SCHEME 3



in Scheme 3. A reasonable starting point would be a sequence based on the well-known properties of malondialdehyde **1**.[7] This highly reactive intermediate is indeed known to very easily give Knoevenagel derivative **14** (Scheme 5). Unfortunately, the use of this adduct is limited due to its high instability resulting from addition of a third molecule of malondialdehyde to give cyclic trimer **15**.

In contrast, Tietze and co-workers have reported[8] that the monoprotected analogue **16** afforded Knoevenagel adduct **17**, again rather unstable, but which gave, after reaction with enol ethers **18**, cycloadducts such as **19** (Scheme 6).[9]

By using this approach, aldehydes **19a**,**b** were synthesized following the reported procedures in 60% and 48% yield, respectively. Considering Scheme 3, this sequence corresponds to the condensation of two dialdehydes **1** and aldehyde **3**.

Reaction of aldehyde **19a** with the anion of the silylimino derivative **20**[10] gave, after hydrolysis, the new aldehyde **21** as a mixture of two diastereoisomers in practically equal ratio (undefined geometry for the external double bond). This product can be considered as an equivalent of the key tetraaldehyde **7** (cf. also Scheme 4).

The next sequence addressed the question of the reactivity of aldehyde **21** toward primary amines (corresponding to **5** and **6**). The results are summarized in Scheme 8. The imino derivative **22** was readily obtained from *n*-butylamine. This derivative was not isolated but was directly treated with methanesulfonic acid, according to our reported procedure,[5b] to give pyridinium salt **23** in 66% isolated yield. Formation of a second imino derivative **24** followed by reduction afforded amino derivative **25** as a single isomer (undefined stereochemistry), accompanied by diastereoisomeric regioisomers **26a**,**b** (**25**/**26a**/**26b** ratio 82/13/5). Amine **25** was isolated in 50% yield after chromatography on silica gel. Hydrolysis of the acetal and reductive amination finally led to the bicyclic derivative **27**, which was recovered in 70% yield. This product was also isolated in comparable overall yield when the same procedure was conducted without isolation of intermediate amino derivative **25**. Acidic hydrolysis of acetal **25** in the presence of acetone resulted in formation of **28** as two unseparable isomers **28a**/**28b** in a 3/2 ratio (undefined stereochemistry). Filtration over silica gel resulted in a new equilibrium[11] in favor of isomer **28b** (**28a**/**28b** ratio 1/4). Derivatives **28** possess some structural analogies with the skeleton of sarain 1, another alkaloid extracted from sponges.[12]

A brief investigation of the reaction of aldehyde derivative **19b** with a primary amine in acidic medium, followed by $NaBH_4$ reduction, is presented in Scheme 9. The only product isolated was the olefinic piperidine **30**, a mixture of two diastereoisomers in 1/1 ratio, resulting presumably from the reduction of an intermediate 1,4-dihydropyridine **29**.

Finally, we investigated the reaction sequence starting from substituted aldehyde **19b** (Scheme 10). Reaction with imino derivative **29**, under the conditions used for preparation of aldehyde **21**, led to aldehyde **31**, isolated in 82% yield as a mixture of diastereoisomers. This

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(7) Gomez-Sanchez, A.; Hermosin, I.; Lassaletta, J.-M.; Maya, I. *Tetrahedron* **1993**, *49*, 1237−1250 and references therein.

(8) (a) Tietze, L. F.; Meier, H.; Nutt, H. *Liebigs Ann. Chem.* **1990**, 253−260. (b) Tietze, L. F.; Meier, H.; Nutt, H. *Chem. Ber.* **1989**, *122*, 643−650. (c) Tietze, L. F.; Glüsenkamp, K. H.; Holla, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 793−794.

(9) Noteworthy is the fact that one such iridoid derivative, loganin, is a precursor of the biosynthesis of thousands of natural alkaloids. For a review, see: Szantay, C.; Honty, K. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley: Chichester, UK, 1994; Chapter 4.

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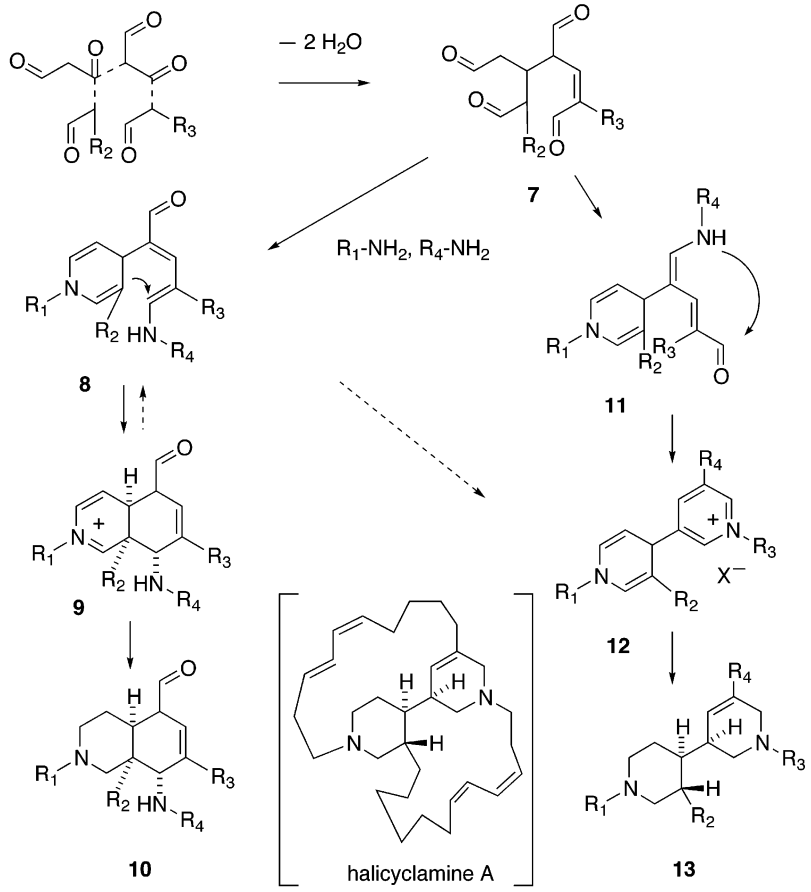
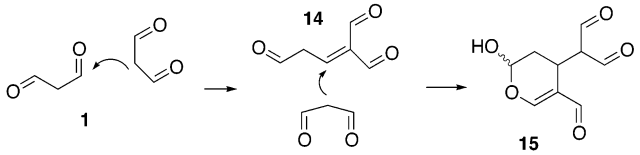
(11) Similar reversible equilibria have been observed for analogous *β*-amino-ketones, see for example: Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528−4532 and references therein.

(12) Cimino, G.; Spinella, A.; Trivellone, E. *Tetrahedron Lett.* **1989**, *30*, 133−136.

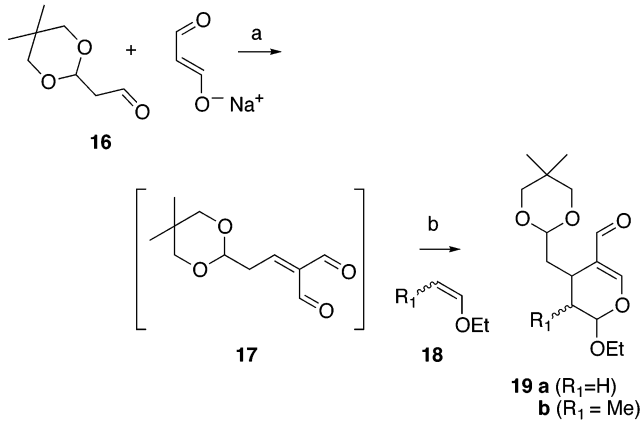
SCHEME 4



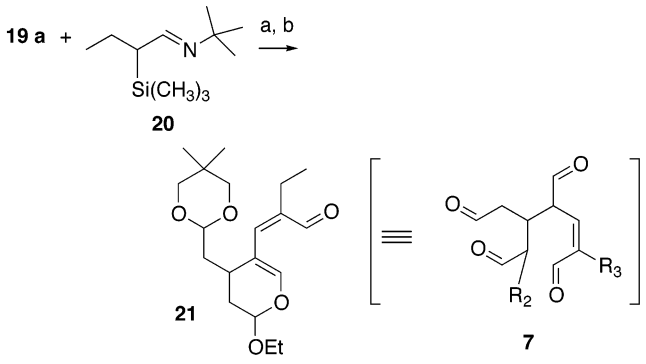
SCHEME 5



SCHEME 6



SCHEME 7[a]

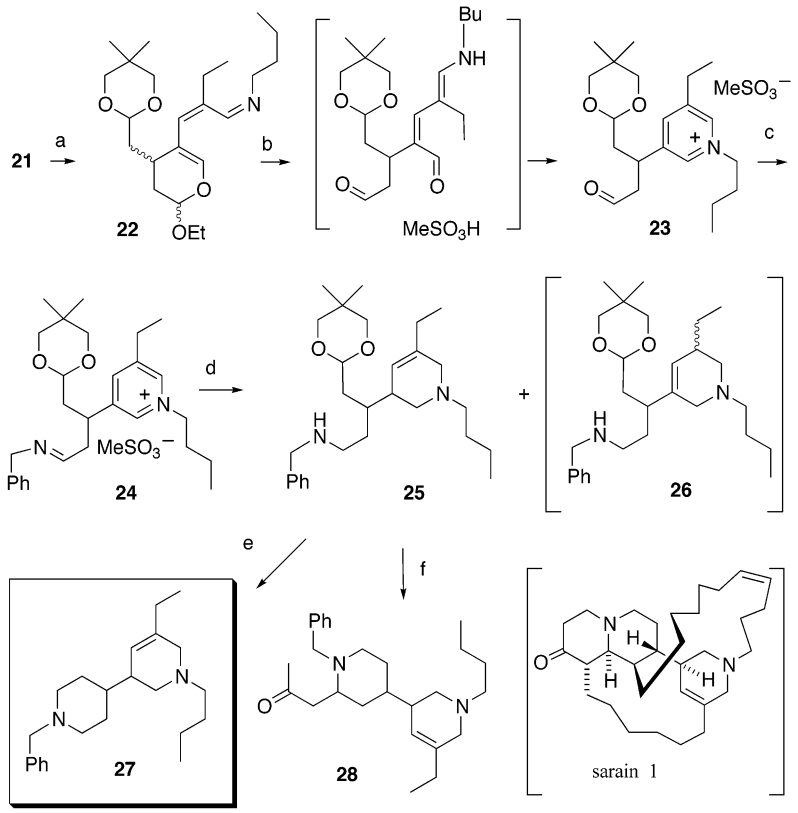


[a] Reagents and conditions: (a) LDA, THF−HMPA, 0 °C, (b) H_2O; 70% overall yield.

mixture was treated successively with *n*-butylamine to give the corresponding imino derivatives **32** and then by methanesulfonic acid affording finally two isomeric pyridinium salts **33** in 1/1 ratio and 66% yield.

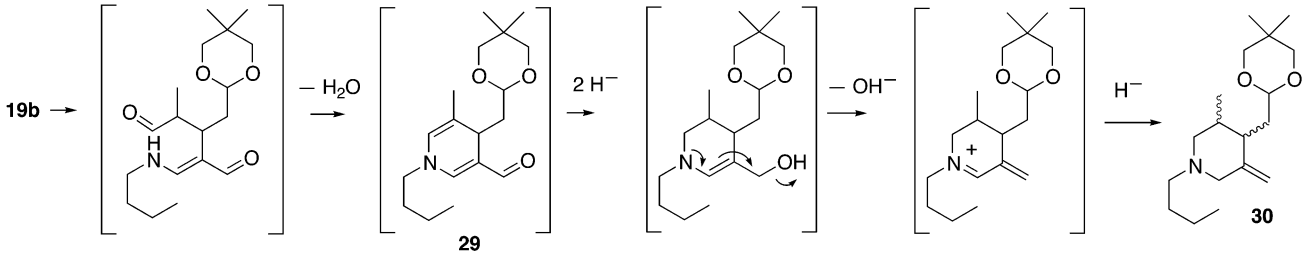
Treatment of salts **33** under the conditions used for the preparation of halicyclamine analogue **27** yielded the four new bicyclic derivatives **35a**−**d** in 16/27/47/9 ratio. The structure of compound **35a** was deduced from a comparison with an authentic sample.[5b] The stereochemical assignments for the other isomers were made after a comparison of the ^{1}H NMR signals of the benzylic protons. These two protons appeared as singlets in isomers **35a** and **35b** and as two distinct doublets in isomers **35c** and **35d**. According to unambiguous data from the literature,[13] this clearly established a trans relationship for substituents at the 3 and 4 positions of the *N*-benzyl piperidine ring in **35a**/**35b** and a cis relationship for these substituents in **35c**/**35d**. These

SCHEME 8[a]



[a] Reagents and conditions: (a) $BuNH_2$, 3Å molecular sieves, MeOH, 60 °C; (b) $MeSO_3H$, 60 °C, 66% overall yield for **23**; (c) $BnNH_2$, 3Å molecular sieves, MeOH, 60 °C; (d) $NaBH_4$, MeOH, 50% yield for **25**; (e) 2 N HCl, dioxane then $NaBH_4$;(f) TsOH, acetone, H_2O.

SCHEME 9



data were, however, insufficient to distinguish these last two isomers. Noteworthy is the fact that some natural bis-piperidine analogues of halicyclamine A feature the 3,4 cis arrangement of the piperidine ring as in **35c**/**35d**.[14]

Conclusion

In conclusion, we have shown that it is possible to make use of the condensation reactions of Scheme 3, involving malondialdehyde, two aldehydes, and two primary amines, for a practical access to analogues of the natural sponge alkaloid halicyclamine A (**27**, **35**). The same procedure also allowed final introduction of a keto derivative leading to adducts having some features of sarain 1 (**28**). The synthetic route implicates nine reactions which can be conducted in only four steps involving consecutive reactions **16** → **19a** → **21** → **23** → **27** (analogous sequences for **35a**−**d**). Bicyclic derivative **35** was produced as a diastereoisomeric mixture due to the lack of selectivity observed for the reduction of open-chain intermediate **33**. For future synthetic purposes it will be necessary to access, by a variation of the reported procedure, intermediate **36** whose reduction has been reported by us[5b] to be highly selective (leading to halicyclamine A relative stereochemistry). The main present limitation is the difficulty encountered in the cycloaddition reaction of the Knoevenagel derivative **17** with other enol ethers **18**, in particular those substituted by a long lipophilic R_1 alkyl chain.

Considering the synthetic route depicted in Scheme 4, based upon a biogenetic proposal, it can be noted that while analogues of tetraaldehydes **7** (**21**, **31**) have been obtained and shown to lead to bicyclic derivatives **13**, the formation of manzamine A-like adduct **10** was not

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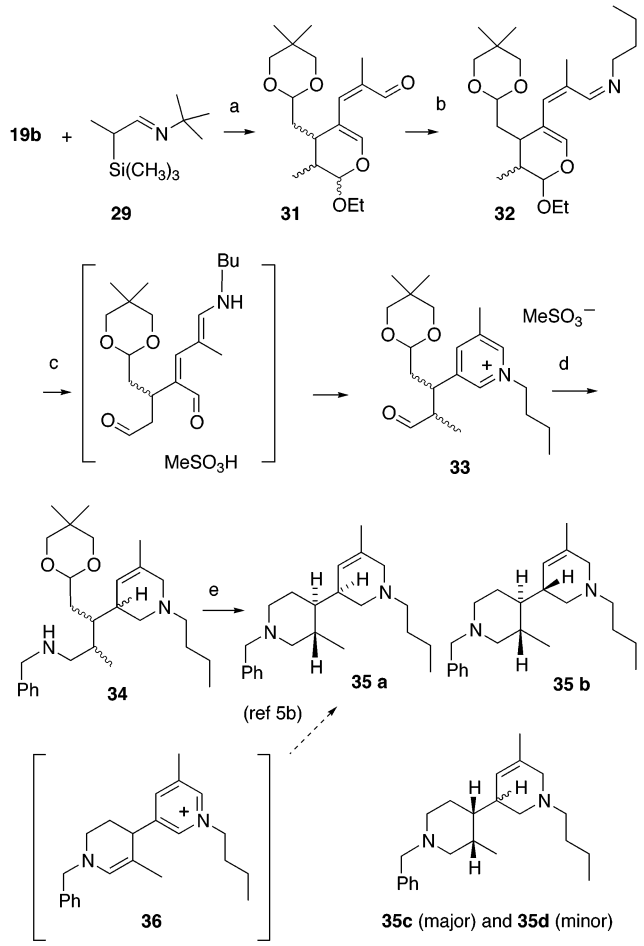
(14) (a) Mary J.; Brereton, I. M.; Willis, A. C.; Hooper, J. N. A. *Tetrahedron* **1996**, *52*, 9111−9120. (b) Clark, R. J.; Field, K. L.; Charan, R. D.; Garson, M. J.; Brereton, I. M.; Willis, A. C. *Tetrahedron* **1998**, *54*, 8811−8826. (c) Torres, Y. R.; Berlinck, R G. S.; Magalhaes, A; Schefer, A B.; Ferreira, A. G.; Hajdu, E.; Muricy, G *J. Nat. Prod*. **2000**, *63*, 1098−1105.

SCHEME 10[a]



[a] Reagents and conditions: (a) LDA, THF−HMPA, 82% yield; (b) $BnNH_2$, 3Å molecular sieves, MeOH, reflux; (c) $MeSO_3H$, MeOHn reflux, 66% yield from **31**; (d) $BnNH_2$, 3Å molecular sieve, MeOH reflux, then $NaBH_4$; (e) 2 N HCl, dioxane, then $NaBH_4$, 55% yield (mixture of **35a**/**35b**/**35c**/**35d** in 16/27/47/9 ratio).

observed. We believe that the difficulty encountered in the formation of this product is likely to be due to the reversibility of formation of adducts such as **9**, while the formation of pyridinium salts such as **12** is irreversible.

Research concerning the applications in natural product synthesis of the multicomponent assembly depicted in Scheme 3 is currently underway in our laboratory.

Experimental Section

4-(5,5-Dimethyl[1,3]dioxan-2-yl-methyl)-6-ethoxy-5,6-dihydro-4*H*-pyran-3-carbaldehyde (19a). A solution of aldehyde **16** (2 g, 12.6 mmol) and malondialdehyde sodium salt (2.12 g, 16.4 mmol), in H_2O (20 mL), was stirred, under a nitrogen atmosphere, during 48 h at 5 °C. The resulting mixture was allowed to warm to 20 °C and ethyl vinyl ether **18a** (4 0.24 mL, 44.3 mmol), in 1,2-dichloroethane, was added dropwise followed by portionwise addition of $NaH_2PO_4 \cdot 2H_2O$ (7.59 g). After stirring at rt for 2 h the solution was neutralized with sodium bicarbonate (6.3 g) and diluted with H_2O (30 mL). Extraction with CH_2Cl_2 (3 × 30 mL) and the usual workup gave a residue that was chromatographed over silica gel with AcOEt/heptane (20/80) as eluent. Aldehyde **19a** was isolated as a mixture of two isomers in approximately 1:1 ratio (pale yellow oil, 5.5 g, 60% yield). Mixture of the two isomers: IR (film) 1673, 1145 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) characteristic signals at δ 5.22 (dd, J = 3, 4 Hz, 1H) and 5.23 (dd, J = 3, 3 Hz, 1H), 7.18 (s, 1H) and 7.19 (s, 1H), 9.22 (s, 1H) and 9.23 (s, 1H) (see Supporting Information for details); ^{13}C NMR (CD_3OD, 75 MHz) δ 15.2 (2 × 1C), 22.0−22.5, 23.2−23.5, 30.2 (2 × 1C), 30.8−31.7, 38.2−38.9, 65.1−65.4, 77.3 (2 × 1C), 100.1−100.4, 101.4−101.6, 122.7−123.3, 162.7−163.3, 190.0−190.6; SM (EI) m/z 284 ($M^{+\bullet}$), 255, 182; HRMS (CI, isobutane) calcd for $C_{15}H_{25}O_5$ (MH^+) 285.1702, found 285.1706.

4-(5,5-Dimethyl[1,3]dioxan-2-yl-methyl)-6-ethoxy-5-methyl-5,6-dihydro-4*H*-pyran-3-carbaldehyde (19b). This aldehyde was obtained from aldehyde **16** (7.9 g, 50 mmol), malondialdehyde sodium salt (8.4 g, 65 mmol), and vinyl ether **18b** (mixture of *E* and *Z* isomers, 19.3 mL, 175 mmol) by the procedure used for the preparation of aldehyde **19a**. Aldehyde **19b** was recovered, after chromatography over silica gel (AcOEt/heptane, 20/80), as a colorless oily mixture of four diastereoisomers (ratio 47/35/14/4, 7.12 g, 48% yield): IR (film) 1674, 1119 cm^{-1}; SM (EI) m/z 298 ($M^{+\bullet}$), 269, 196; HRMS (CI, isobutane) calcd for $C_{16}H_{26}O_5$ (MH^+) 298.1780, found 298.1792. A sample of the major isomer was isolated by chromatography over silica gel for NMR analysis: ^1H NMR ($CDCl_3$, 250 MHz) δ 0.71 (s, 3H), 0.85 (d, J = 7 Hz, 3H), 1.17 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.65 (dt, J = 5, 8 Hz, 1H), 1.90 (dt, J = 5, 8 Hz, 1H), 2.25 (m, 1H), 2.60 (m, 1H), 3.33−3.60 (m, 4H), 3.65, (q, J = 7.5 Hz, 2H), 4.01 (dd, J = 7.1, 7.1 Hz, 1H), 4.56 (t, J = 5 Hz, 1H), 5.04 (d, J = 2.5 Hz, 1H), 7.21 (s, 1H), 9.26 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 11.5, 15.0, 21.8, 23.1, 30.1, 31.7, 34.0, 39.7, 65.7, 77.2, 101.2, 101.9, 121.2, 162.9, 190.6. HRMS (CI, isobutane) calcd for $C_{16}H_{27}O_5$ (MH^+) 299.1859, found 285.1862.

3-[4-(5,5-Dimethyl[1,3]dioxan-2-yl-methyl)-6-ethoxy-5,6-dihydro-4*H*-pyran-3-yl]-2-ethyl-propenal (21). To a solution of LDA, freshly prepared from *n*-butyllithium (1.6 M in hexane, 11.2 mL) and diisopropylamine (2.57 mL, 18.3 mmol) in THF (4 mL), was added dropwise, at 0 °C and under a nitrogen atmosphere, a solution of iminoderivative **20**, in THF (4 mL). The resulting mixture was stirred at 0 °C for 1 h. Hexamethylphosphotriamide (3.06 mL, 17.6 mmol) was then added, followed after 0.2 h by dropwise addition of aldehyde **19a** (2 g, 7.0 mmol) in THF (4 mL) over a period of 0.5 h. After 1 h at ambient temperature under stirring, the resulting mixture was hydrolyzed with H_2O (50 mL). Extraction with Et_2O (3 × 50 mL) and washing of the combined organic phase with a saturated NaCl aqueous solution gave after the usual workup and chromatography over silica gel (AcOEt/heptane, 10/90) aldehyde **21** as a mixture of two isomers in practically 1:1 ratio (colorless oil, 1.65 g, 70% yield). Mixture of the two isomers: IR (film) 1677, 1139 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) characteristic signals at δ 4.49 (dd, J = 4, 4 Hz, 2 × 1H), 5.07 (m, 2 × 1H), 6.52 (s, 2 × 1H), 6.75 (s, 1H), and 6.76 (s, 1H) (see Supporting Information for details); ^{13}C NMR (CD_3OD, 75 MHz) δ 13.4 (2 × 1C), 15.2 (2 × 1C), 18.3 (2 × 1C), 21.9 (2 × 1C), 23.0 (2 × 1C), 27.3−27.9, 30.2 (2 × 1C), 31.1−32.0, 38.8−39.8, 64.5−64.8, 77.2 (2 × 2C), 97.4−98.2, 100.4 (2 × 1C), 115.0−115.4, 140.6−140.8, 146.4−147.3, 149.1−149.6, 195.3 (2 × 1C); MS (CI) m/z 339 (MH^+), 293, 163, 115; HRMS (CI, isobutane) calcd for $C_{19}H_{31}O_5$ (MH^+) 339.2170, found 339.2150.

1-Butyl-3-[1-(5,5-dimethyl[1,3]dioxan-2-yl-methyl)-3-oxo-propyl]-5-ethyl-pyridinium Methanesulfonate (23). A solution of aldehyde **21** (1.43 g, 4.2 mmol) and *n*-butylamine (1.25 mL, 12.6 mmol), in MeOH (70 mL) and in the presence of 3 Å molecular sieves, was refluxed for 2 h. Methanesulfonic acid (0.55 mL, 8.4 mmol) was added to the resulting mixture and the solution was further refluxed overnight. Removal of solvent and chromatography over silica gel ($MeOH/CH_2Cl_2$, 15/85) afforded pyridinium salt **23** as a gum (1.24 g, 66% yield): IR (film) 1717, 1395, 1197 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 3H), 0.93 (t, J = 7.5 Hz, 3H), 1.01 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.35 (m, J = 5, 7 Hz, 2H), 1.96 (m, J = 5, 5 Hz, 2H), 2.15 (m, 2H), 2.74 (s, 3H), 2.87 (q, J = 7.2 Hz, 2H), 3.10 (dd, J = 2 Hz, 7 Hz, 1H), 3.2−3.5 (m, 5H), 3.73 (m, 1H), 4.36

(t, J = 4.5 Hz, 1H), 4.79 (m, 2H), 8.09 (s, 1H), 8.72 (s, 1H), 9.04 (s, 1H), 9.65 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 13.7, 14.6, 19.3, 21.7, 23.0, 25.9, 30.0, 32.6, 33.8, 39.3, 39.6, 49.4, 61.7, 77.4 (2C), 99.9, 141.4, 142.3, 144.1, 144.4, 146.0, 200.5; MS (ESI) m/z 348 (M^+).

Benzyl[3-(1-butyl-5-ethyl-1,2,3,6-tetrahydro-pyridin-3-yl)-4-(5,5-dimethyl[1,3]dioxan-2-yl)-butyl]amine (25). A solution of pyridinium salt **23** (0.9 g, 2 mmol) and benzylamine (0.33 mL, 3 mmol), in MeOH (35 mL), was refluxed over 3 Å molecular sieves for 2 h. The resulting imino derivative **24** was not isolated, but was directly reduced at ambient temperature by addition of an excess of sodium borohydride, followed by stirring of the resulting mixture overnight. The usual workup left a gum (mixture of amino derivative **25** and two isomeric amines **26** in a 82/13/5 ratio as determined by GC). Chromatography over silica gel (AcOEt/heptane, 50/50) allowed separation of major amino derivative **25** as a colorless oil (442 mg, 1 mmol, 50% yield): IR (film) 1455, 1119, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H), 1.16 (s, 3H), 1.30 (q, J = 7.5 Hz, 2H), 1.48−1.67 (m), 1.98 (m, 3H), 2.42 (t, J = 7.5 Hz, 2H), 2.55 (m, 1H), 2.65 (m, 3H), 2.78 (dt, J = 5.5, 11 Hz, 1H), 3.02 (d, J = 13 Hz, 1H), 3.35 (d, J = 11 Hz, 2H), 3.55 (d, J = 11 Hz, 2H), 3.78 (s, 2H), 4.45 (t, J = 5 Hz, 1H), 5.26 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 12.1, 14.0, 20.7, 21.7, 23.0, 27.8, 29.0, 30.0, 31.5, 34.3, 36.6, 38.1, 47.6, 52.9, 53.7, 55.8, 58.2, 77.1, 101.3, 120.7, 126.9, 128.1, 128.3, 138.4, 139.8; HRMS (CI, isobutane) calcd for $C_{28}H_{47}N_2O_5$ (MH^+) 443.3635, found 443.3635.

1-Benzyl-1-butyl-5-ethyl-1,2,3,6,1,2,3,4,5,6-decahydro-[3,4]bipyridinyl (27). A solution of amino derivative **25** (440 mg, 1 mmol) and aqueous 2 N HCl (13 mL), in dioxane (13 mL), was heated at 50 °C overnight. The resulting mixture was allowed to cool to room temperature and sodium borohydride (0.33 g, 8.8 mmol) was then added portionwise. After 5 h under stirring, the solvent was evaporated under reduced pressure, H_2O was added, and the product was extracted with CH_2Cl_2. The usual workup gave a residue that was chromatographed over silica gel (heptane/AcOEt 50/50) to give pure bicyclic derivative **27** (240 mg, 0.7 mmol, 70% yield) as a colorless oil: IR (film) 1494, 1456, 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.8 Hz, 3H), 1.30 (q, J = 7.8 Hz, 2H), 1.33 (m, 3H), 1.52 (q, J = 7.8 Hz, 2H), 1.59 (dt, J = 3, 13 Hz, 2H), 1.71 (dt, J = 3, 13 Hz, 2H), 1.91 (dt, J = 3, 15 Hz, 2H), 1.97 (q, J = 7.5 Hz, 2H), 2.07 (m, 2H), 2.37 (t, J = 7.8 Hz, 2H), 2.64 (m, 2H), 2.88 (m, 2H), 2.95 (d, J = 15 Hz, 1H), 3.47 (s, 2H), 5.40 (s, 1H), 7.25 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4, 14.2, 20.9, 28.0, 29.4, 29.6, 29.7, 39.5, 40.6, 53.8, 54.2, 56.3, 58.5, 63.6, 120.7, 126.9, 128.1, 129.2, 138.1, 138.6; SM (CI) m/z 341 (MH^+), 249; HRMS (CI, isobutane) calcd for $C_{25}H_{37}O_2$ (MH^+) 341.2956, found 341.2943.

1-(1-Benzyl-1-butyl-5-ethyl-1,2,3,6,1,2,3,4,5,6-decahydro-[3,4]bipyridinyl-2-yl)-propan-2-one (28). A solution of amino derivative **25** (75 mg, 0.17 mmol), in a mixture of acetone/H_2O (1/4, 6 mL), was refluxed for 30 h in the presence of pyridinium p-toluenesulfonate (40 mg, 0.16 mmol) and p-toluenesulfonic acid (126 mg, 0.66 mmol). The resulting mixture was neutralized with a saturated solution of aqueous sodium bicarbonate. Extraction with CH_2Cl_2 followed by the usual workup gave crude adduct **28**, which was found to be a mixture of two unseparable diastereoisomers **28a** and **28b** in an approximate ratio of 3/2 respectively as determined by ^{1}H NMR spectroscopy (CH_3CO signals). Filtration over silica gel (MeOH/CH_2Cl_2 1/99) resulted in equilibration in favor of diastereoisomer **28b** (**28a**/**28b** 1/4, 30 mg, 45% yield): IR (film) 1710, 1494, 1353 cm^{-1}; SM (ESI) m/z 397 $(MH)^+$, 339; HRMS (CI, isobutane) calcd for $C_{26}H_{41}N_2O$ (MH^+) 397.3219, found 397.3232. NMR data for the major isomer (**28b**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 6.9 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H), 1.36 (m, 4H), 1.50 (m, 5H), 1.96 (m, 4H), 2.09 (m, 5H), 2.40 (q, J = 7.2 Hz, 2H), 2.61 (m, 4H), 2.90 (m, 1H), 3.4−3.6 (m, 4H), 5.38 (s, 1H), 7.28 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.3, 14.0, 20.8, 27.9, 28.3, 29.2, 30.6, 32.2, 33.9, 39.9, 40.3, 45.7, 53.5, 54.2, 56.1, 58.3, 58.9, 120.4, 126.9, 128.2, 129.6, 138.1, 139.4, 208.8; HRMS (CI, isobutane) calcd for $C_{26}H_{41}N_2O$ (MH^+) 397.3219, found 397.3215.

1-Butyl-4-[5,5-dimethyl[1,3]dioxan-2-yl-methyl]-3-methylene-piperidine (30). A solution of aldehyde **19a** (0.18 g, 0.6 mmol), n-butylamine (0.12 mL, 1.2 mmol), and 2 N HCl (0.2 mL) in MeOH (5 mL) was refluxed overnight. After removal of solvents under reduced pressure, the resulting mixture was dissolved in MeOH and an excess of $NaBH_4$ was added. After overnight stirring at ambient temperature, the usual workup left a gum that was chromatographed over alumina (AcOEt/heptane: 10/90). Piperidine **30** was obtained as a mixture of two isomers (0.50 g, 28% yield): IR (film) 1649, 1468, 1393, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (s, 3H), 0.86 (m, 6H), 1.17 (s, 3H), 1.20 (q, J = 7.5 Hz, 2H), 1.47 (q, J = 7.5 Hz, 2H), 1.6−1.8 (m, 2H), 1.95 (m, 1H), 2.36 (m, 4H), 2.59 (dd, J = 3, 11 Hz, 1H), 2.76 (m, 1H), 2.96 (m, 1H), 3.38 (m, 2H), 3.50 (m, 2H), 4.41 (dd, J = 3, 4 Hz, 1H), 4.50 (t, J = 6 Hz, 1H), 4.55 (t, J = 6 Hz, 1H), 4.71 (d, J = 14.5 Hz, 2H), 4.80 (d, J = 6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 and 14.7, 18.6, 20.9, 21.9, 23.1, 29.3, 30.2 and 30.3, 31.9 and 33.8, 35.5 and 35.6, 40.9 and 43.4, 53.0 and 58.1, 58., and 58.8, 59.2 and 60.0, 77.4 (2C), 101.1 and 101.3, 110.0 and 110.2, 146.0; HRMS (CI, isobutane) calcd for $C_{18}H_{34}NO_2$ (MH^+) 296.2572, found 296.2589.

3-[4-(5,5-Dimethyl[1,3]dioxan-2-yl-methyl)-6-ethoxy-5-methyl-5,6-dihydro-4*H*-pyran-3-yl]-2-methyl-propenal (31). To a solution of LDA, freshly prepared from n-butyllithium (1.6 M in hexane, 13.4 mL) and diisopropylamine (3 mL, 21.8 mmol) in THF (5 mL), was added dropwise, at 0 °C and under a nitrogen atmosphere, a solution of imino derivative **29** (3.88 g, 21 mmol), in THF (5 mL). The resulting mixture was stirred at 0 °C for 1 h. Hexamethylphosphotriamide (3.64 mL, 21 mmol) was then added, followed after 0.2 h by dropwise addition of aldehyde **19b** (2.5 g, 8.4 mmol) in THF (5 mL) over a period of 0.5 h. After 1 h at ambient temperature under stirring, the resulting mixture was hydrolyzed with H_2O (50 mL). Extraction with Et_2O (3 × 50 mL) and washing of the combined organic phase with a saturated NaCl aqueous solution gave after the usual workup and chromatography over silica gel (AcOEt/heptane 10/90) aldehyde **31** as a mixture of isomers (colorless oil, 2.31 g, 82% yield). Mixture of isomers (see Supporting Information for ^{1}H NMR): IR (film) 1674, 1162 cm^{-1}; HRMS (CI, isobutane) calcd for $C_{19}H_{31}O_5$ (MH^+) 339.2172, found 339.2175. A small quantity of one of the major isomer was isolated by chromatography over silica gel: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (s, 3H), 0.97 (d, J = 7.5 Hz, 3H), 1.17 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H), 1.71 (m, 1H), 1.83 (m, 1H), 1.91 (s, 3H), 2.16 (m, 1H), 2.50 (m, 1H), 3.37 (d, J = 11 Hz, 2H), 3.60 (d, J = 11 Hz, 2H), 3.64 (q, J = 7.5 Hz, 1H), 3.97 (q, J = 7.5 Hz, 1H), 4.49 (t, J = 5 Hz, 1H), 4.95 (d, J = 2.1 Hz, 1H), 6.61 (s, 1H), 6.82 (s, 1H), 9.36 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.0, 12.0, 15.1, 21.8, 22.9, 30.1, 34.1, 36.9, 40.4, 65.3, 77.1, 77.2, 99.4, 100.1, 113.7, 133.9, 148.5, 150.5, 195.1; HRMS (CI, isobutane) calcd for $C_{19}H_{31}O_5$ (MH^+) 339.2172, found 339.2173.

1-Butyl-3-[1-(5,5-dimethyl[1,3]dioxan-2-yl-methyl)-2-methyl-3-oxo-propyl]-5-methyl-pyridinium Methanesulfonate (33). A solution of aldehyde **31** (1.0 g, 2.96 mmol) and n-butylamine (0.87 mL, 8.87 mmol), in MeOH (50 mL), was refluxed over 3 Å molecular sievesfor 2 h. Methanesulfonic acid (0.38 mL, 5.9 mmol) was added to the resulting mixture and the solution further refluxed overnight. Removal of solvent followed by chromatography over silica gel (MeOH/CH_2Cl_2, 15/85) afforded pyridinium salt **33**, which was isolated as a mixture of two isomers in approximately 1:1 ratio (850 mg, 65% yield). Mixture of isomers **33**: IR (film) 1718, 1633, 1196 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (2 × 3H), 0.90 and 0.94 (t, J = 7.3 Hz, 3H), 0.99 and 1.15 (d, J = 7.1 Hz, 3 H), 1.35 (m, 2 × 2H), 2.00 (m, 2 × 2H), 2.14 (m, 2 × 2H), 2.60 and 2.61 (s, 3H), 2.75 (s, 2 × 3H), 2.98 and 3.11 (q, J = 6.6 Hz,

1H), 3.28 (m, 2 × 2H), 3.44 (m, 2 × 2H), 3.58 and 3.67 (m, 1H), 4.25 and 4.33 (t, J = 6.6 Hz, 1H), 4.80 (t, J = 7 Hz, 2 × 2H), 8.01 and 8.07 (s, 1H), 8.88 and 8.94 (s, 1H), 9.07 and 9.17 (s, 1H), 9.60 and 9.66 (s, 1H), 36 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$), see Supporting Information; SM (ESI) m/z 348 (M^+).

Halicyclamine A Analogues (35a−d). Amino derivatives **34** (four diastereoisomers, 62 mg, 62% yield, see Supporting Information for the ^{1}H NMR spectrum of the diastereoisomeric mixture) were obtained from pyridinium salts **33** (100 mg, 0.22 mmol) according to the procedure used for the preparation of amino derivative **25**. These amino derivatives (100 mg, 0.22 mmol) were treated according to the procedure used for the preparation of **27** to give halicyclamine A diastereoisomeric analogues **35a**, **35b**, **35c** (major), and **35d** (minor) (42 mg, 55% yield) as a mixture of four diastereoisomers in a 16/27/47/9 ratio as determined by integration of olefinic proton signals in the ^{1}H NMR spectrum of the crude mixture. Mixture of isomers: IR (film) 1455, 1633, 1196 cm^{-1}); MS (CI) m/z 341 (MH^+), 249, 186, 91; HRMS (CI, isobutane) calcd for $C_{23}H_{37}N_2$ (MH^+) 341.2957, found 341.2958. Careful chromatography over silica gel allowed separation of a small quantity of the four isomers. Isomer **35a**: ^{1}H NMR ($CDCl_3$, 300 MHz) and ^{13}C NMR (75.5 MHz, $CDCl_3$) spectra superimposable to the corresponding spectra of an authentic sample.[5b] Isomer **35b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (d, J = 7 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H), 1.15−1.60 (m, 7H), 1.56 (s, 3H), 1.79 (ddd, J = 2.5, 11, 11 Hz, 1H), 1.97 (dd, J = 9.6, 9.9 Hz, 1H), 2.28 (dt, J = 2, 8 Hz, 2H), 2.53 (m, 3H), 2.74 (m, 2H), 2.89 (d, J = 15.3 Hz, 1H), 2.92 (br d, J = 15.3 Hz, 1H), 3.36 (s, 3H), 5.29 (br s, 1H), 7.17 (m, 5H). Isomer **35c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, J = 7 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 1.15−1.33 (m, 4H), 1.35−1.52 (m, 4H), 1.58 (s, 3H), 1.68−2.08 (m, 6H), 2.19−2.41 (m, 2H), 2.48−2.67 (m, 3H), 2.75−2.88 (m, 2H), 3.26 (d, J = 13 Hz, 1H), 3.42 (d, J = 13 Hz, 1H), 5.42 (br s, 1H), 7.10−7.36 (m, 5H). Isomer **35d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 7 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H), 1.59 (s, 3H), 2.80−2.91 (m, 1H), 3.00 (br d, J = 17 Hz, 1H), 3.14 (br d, J = 14.5 Hz, 1H), 3.27 (d, J = 13 Hz, 1H), 3.43 (d, J = 13 Hz, 1H), 5.56 (br s, 1H), 7.12−7.37 (m, 5H).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of derivatives **19a**,**b**, **21**, **23**, **25**, **27**, **30**, **31**, and **33** with attribution of signals, and ^{1}H NMR spectra of derivatives **28**, **34**, and **35a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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