JOC*Note*

New Polycyclic Diamine Scaffolds from Dimerization of 3-Alkyl-1,4-dihydropyridines in Acidic Medium

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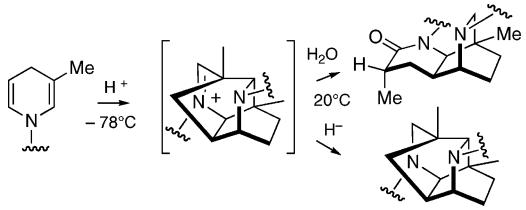
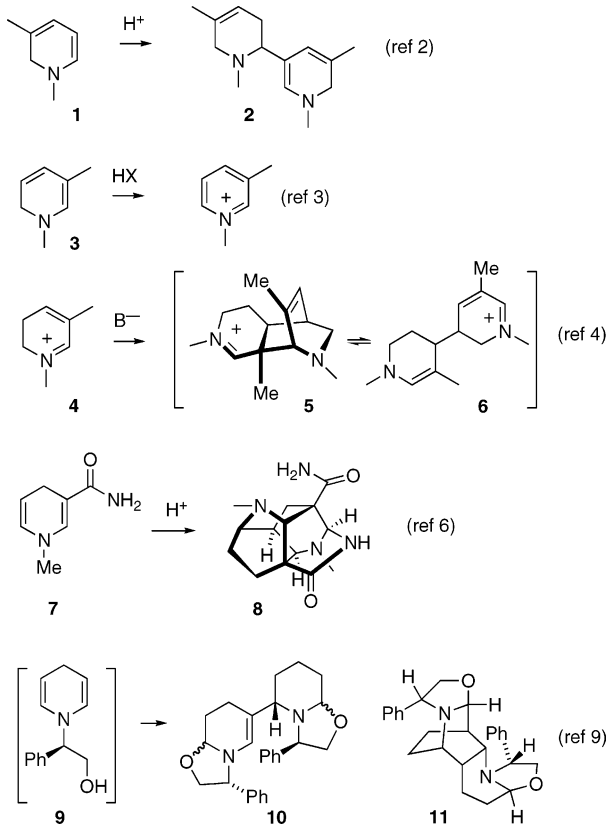


3-Alkyl-1,4-dihydropyridines dimerize in acidic medium, at low temperature, to give polycyclic imminium salts derivatives that were reduced to afford new polycyclic diamine scaffolds. The reaction can be extended to enantiopure series starting from *R*-(+)- or *S*-(−)-1-phenylethylamine. Long exposure of the polycyclic imminium salt intermediates to air moisture at 20 °C resulted in formation of new amide derivatives. This is probably due to the addition of water followed by an intramolecular oxido-reduction process.

Dihydropyridines[1] not stabilized with electro-withdrawing substituents are very unstable compounds that have a strong tendency to give untractable polymers in the presence of protons. Air moisture is generally sufficient to initiate this process, which can be catalytic.

Substitution with alkyl groups at position 3 has a significant stabilizing effect that allows competitive formation of two different kinds of compounds, pyridiniums salts and tetrahydropyridines, resulting from oxido-reduction processes, or products resulting from formation of dimeric adducts (Scheme 1). The outcome of these reactions depends strongly on the regiochemistry of the dihydropyridine double bonds. Thus, 1,2-dihydropyridines **1** were found to dimerize, giving adducts **2**,[2] while the corresponding 1,6 isomers **3**, when treated with acids, prefer spontaneous oxidation to the corresponding pyridinium salts.[3] On the other hand, 5,6-dihydropyridinium salts **4**, when deprotonated with bases, gave adducts **5** and **6**, which can be trapped by borohydride reduction. This dimerization process is reversible, and long reaction times resulted in the irreversible formation of oxido-reduction products (pyridinium salt and tetrahydropyridine).[4]

SCHEME 1. Previous Selected Reactions Illustrating the Diverse Behavior of Unstable Dihydropyridine Intermediates



In this context, few data concerning nonstabilized 1,4-dihydropyridines are available, but the corresponding derivatives stabilized by electro-withdrawing groups at position 3 were known to usually give adducts similar to **2**.[1,5] Interestingly, it was shown early that *N*-methyl-1,4-dihydronicotinamide **7** gave the polycyclic derivative **8** when treated in acidic medium.[6] Photodimerization processes leading to polycyclic derivatives were also reported.[7] The only report concerning nonstabilized 1,4-dihydropyridines was the dimerization of the very unstable intermediate **9**,[8] which was recently reported to give mixtures of dimers **10** and **11**.[9] All data depicted in

(1) For dihydropyridine chemistry reviews, see: Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156 and references therein.

(2) Casini, A.; Di Rienzo, B.; Micheletti Moracci, F.; Tortorella, S.; Liberatore, F.; Arnone, A. *Tetrahedron Lett.* **1978**, 2139−2142.

(3) Marazano, C. Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France. Unpublished observations, 1987.

(4) (a) Gomez, J.-M.; Gil, L.; Ferroud, C.; Gateau-Olesker, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2001**, *66*, 4898−4903. (b) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem.−Eur. J.* **1999**, *5*, 3154−3161. (c) Baldwin, J. E.; Bischoff, L.; Claridge, T. D. W.; Heupel, F. A.; Spring, D. R.; Whitehead, R. *Tetrahedron* **1997**, *53*, 2271−2290. (d) Gil, L.; Baucherel, X.; Martin, M.-T.; Marazano, C.; Das, B. C. *Tetrahedron Lett.* **1995**, 6231−6234.

(5) Anderson, A. G.; Berkelhammer, G. *J. Am. Chem. Soc.* **1958**, *80*, 992−999.

(6) (a) Ammon, H. L.; Jensen, L. H. *J. Am. Chem. Soc.* **1966**, *88*, 613−614. (b) Kühnis, H.; Traber, W.; Karrer, P. *Helv. Chim. Acta* **1957**, *40*, 751−758.

(7) (a) Hilgeroth, A.; Baumeister, U. *Chem.−Eur. J.* **2001**, *7*, 4599−4603. (b) Hilgeroth, A.; Baumeister, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 576−578.

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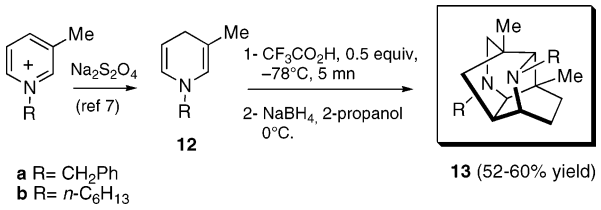
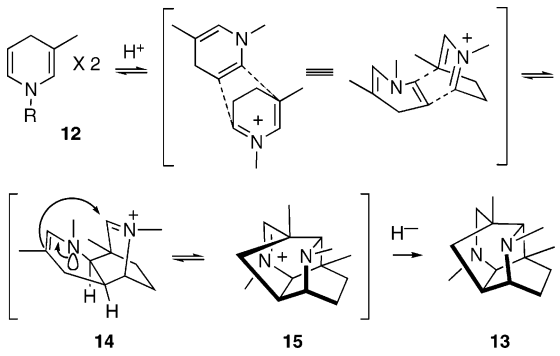
SCHEME 2



SCHEME 3. Proposed Mechanism for the Formation of Adducts 13



Scheme 1 witness the remarkable structural diversity that results from the high reactivity of dihydropyridine intermediates.

In this note, we report new features concerning dimerization of nonstabilized 1,4-dihydropyridines **12** (Scheme 2), now easily available from dithionite reduction of pyridinium salts.[8]

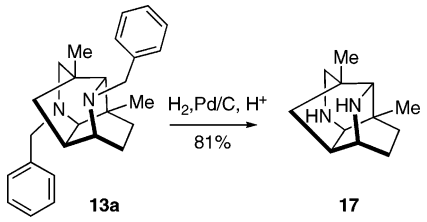
Treatment of dihydropyridines **12a** or **12b** (Scheme 2) at low temperature with trifluoroacetic acid followed by borohydride reduction resulted in the two cases in formation of a single derivative **13a** or **13b**, which was isolated in ca. 50−60% yield.[10]

A proposed mechanism for this reaction is depicted in Scheme 3. Protonation of one dihydropyridine unit gave a 4,5-dihydropyridium salt that cyclized with another 1,4-dihydropyridine to give cycloadduct **14**. Formation of a third carbon−carbon bond furnished iminium salt **15** whose reduction with sodium borohydride gave the observed polycyclic adduct **13**. The only other product isolated from the reaction was the piperidine resulting from complete reduction of dihydropyridine **12**. The reduction product of the cycloaddition intermediate **14** (equivalent to **11**) was not observed.

This process is in fact similar to the one observed for the dimerization of the dihydronicotinamide derivative **7**, but in this last case the iminium intermediate **16** was trapped by the amino group of the amide function (Scheme 4), giving polycyclic derivative **8**.

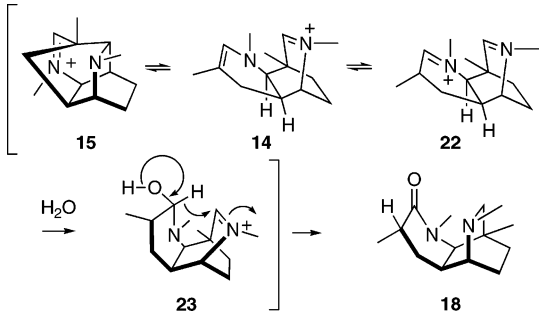
Noteworthy is the fact that catalytic hydrogenation of adduct **13a** afforded diamine scaffold **17** in good yield (Scheme 5).

SCHEME 5



Surprisingly, when dihydropyridine **12a** or **12b** was left after treatment with acid in the above conditions at ambient temperature for 4 days, sodium borohydride reduction did not afford any polycyclic derivatives **13a** or **13b**. The main products isolated were amide **18a** and **18b** (Scheme 6). Avoiding the sodium borohydride reduction, which was unnecessary, these last products were finally recovered in approximately 40% yield in one step from dihydropyridines **9a** and **9b**, respectively. The polar fraction of the reaction starting from the 1,4-dihydropyridine **12b** was analyzed. The only other products isolated in 9% yield were diastereoisomeric pyridinium salts **19b** whose sodium borohydride reduction afforded dienes **20** and **21** in a 4:1 ratio. These two dienes are very likely to result from ring opening of a dihydropyridine intermediate initially formed from salt **19b** (vide infra).

SCHEME 6



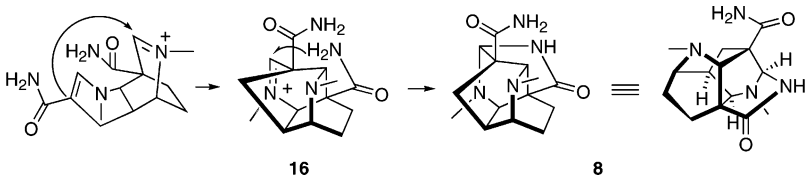
Formation of salts **19b** is presumably the result of an oxido-reduction process following initial dimerization of two 1,4-dihydropyridine units.

The formation of amide **18** can be rationalized (Scheme 7) assuming addition of water on iminium intermediate **22** (in equilibrium with salts **14** and **15**) followed by an intramolecular oxido-reduction process favored by the geometry of intermediate **23**.

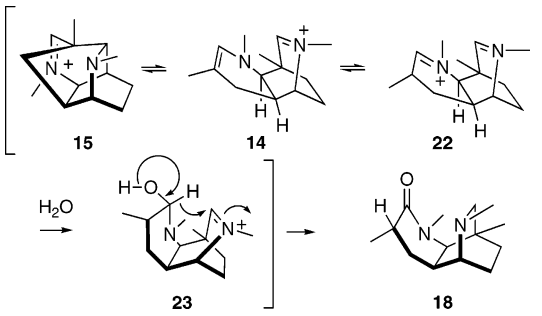
A possible mechanism for the formation of dienes **20** and **21** is depicted in Scheme 8.

The dimerization reaction can be extended to chiral series, starting from 1,4-dihydropyridine **24**[9] (Scheme 9).

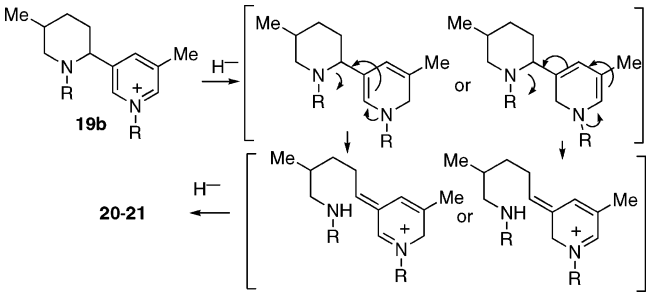
SCHEME 4. Proposed Mechanism for the Formation of Adducts 8



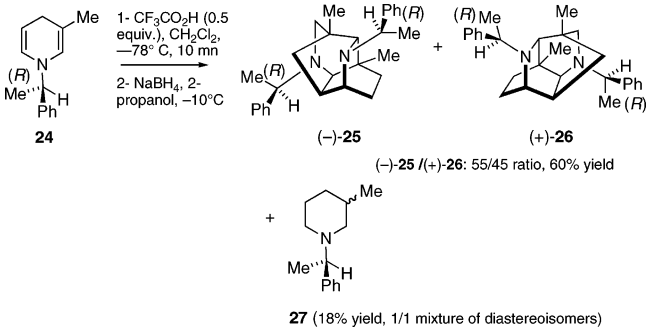
SCHEME 7. Proposed Mechanism for the Formation of Amide 18



SCHEME 8. Proposed Mechanism for the Formation of Dienes 20 and 21



SCHEME 9. Extension to Chiral Series

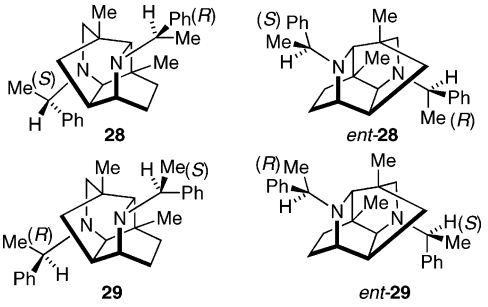


In this case two polycyclic derivatives (−)-**25** and (+)-**26** were obtained, after borohyride reduction, in 60% yield and a 45:55 ratio, respectively. The enantiomeric purity of adduct (−)-**25** was determined as more than 99% by chiral HPLC.[11]

An X-ray analysis of (−)-**25** confirmed structural assignments.

It is crucial to work at low temperature for both the acidic treatment of 1,4-dihydropyridine **24** and the reduction step. Indeed, allowing the reaction mixture to warm to room temperature before borohydride reduction, a procedure used to prepare **13a**,**b**, resulted in racemization of **25** and **26** and, as a consequence, formation of two additional diastereoisomers (±)-**28** and (±)-**29** (Scheme 10) having the two phenylethyl auxiliary groups with the opposite configuration. These derivatives were found to be practically racemic, and this can be rationalized by assuming that racemization of one auxiliary in **25** gives isomers **28** and **29** while the same isomerization in **26** gives *ent*-**28** and *ent*-**29**. As a consequence, compounds **28** and **29** were expected to have very low ee. Again, an X-ray analysis of (±)-**28** allowed us to confirm structure assignments.

SCHEME 10



In summary, 3-alkyl-1,4-dihydropyridines, nonstabilized with electro-withdrawing substituents, react in acidic medium, affording polycyclic scaffolds of general structures **13**. Three carbon−carbon bonds are formed during the reaction. The overall process, starting from 3-picoline, is short (three steps). The extension to chiral series gave enantiomerically pure derivatives. If the diastereoselectivity of the reaction affording (−)-**25** is poor, this is largely compensated again by the simplicity of the procedures and the few steps involved. In addition, intermediates **15** were found to produce new amide derivatives **18** at room temperature as a result of an interesting oxido-reduction process.

Experimental Section

Typical Procedures. Amide Derivative 18a. Trifluoroacetic acid (0.1 mL, 1.35 mmol) was added dropwise to a stirred solution of 1,4-dihydropyridine **12a** (515 mg, 2.78 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C during 2 min. The reaction mixture was then allowed to reach room temperature and stirred for 4 days. The solvent was evaporated, and the crude mixture was chromatographed on alumina using a mixture of ethyl acetate/heptane (2:98) as eluent. Pure amide **18a** was isolated as a colorless oil (216 mg, 42% yield): IR (neat) ν 3075, 3020, 2930, 2870, 1640, 1495, 1450, 1375, 1350, 1235, 1220, 1175, 1125, 1080, 1030, 980, 925 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 0.92 (s, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.29 (m, 1H), 1.37−1.50 (m, 2H), 1.55−1.78 (m, 2H), 1.97 (d, J = 11.1 Hz, 1H), 2.03−2.19 (m, 2H), 2.52 (m, 1H), 2.95 (dd, J = 11.1, 1.9 Hz, 1H), 3.38 (d, J = 11.4 Hz, 1H), 3.60 (d, J = 13 Hz, 1H), 3.70 (d, J = 13 Hz, 1H), 3.72−3.84 (m, 2H), 5.63 (d, J = 15 Hz, 1H), 7.10−7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ (ppm) 16.7, 20.2, 24.8, 33.8, 34.7, 35.8, 36.1, 36.4, 51.2, 57.0, 57.5, 60.5, 61.3, 127.0, 127.4, 128.4, 128.7, 129.3, 138.5, 139.6, 177.2; MS (CI) *m/z* (relative intensity) 389 (MH^+, 100).

Adducts (−)-25 and (+)-26. Trifluoroacetic acid (0.3 mL, 3.9 mmol) was added dropwise to a stirred solution of 1,4-dihydropyridine **12a** (1.53 g, 7.7 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C during 2 min. After 10 min at −78 °C, the resulting mixture was added to a solution of $NaBH_4$ in 2-propanol (25 mL) at −10 °C. The reaction mixture was then allowed to reach room temperature (10 min) and stirred for 15 min. H_2O (50 mL) was carefully added dropwise, and the resulting solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed

(8) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Das, B. C. *Tetrahedron Lett.* **1995**, 707−710.

(9) Francois, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **1997**, *62*, 8914−8916.

(10) All complex structures were resolved by intensive NMR spectroscopy studies including 1D and 2D NMR experiments (COSY 90, NOESY, HMQC, HMBC).

(11) For this purpose, the enantiomer (+)-**25** was synthezised starting from *S*-(−)-1-phenylethylamine. Note that, due to a resolution process resulting from dimerization, the enantiomeric purity of adducts **25** and **26** was expected to be much higher than the enantiomeric purity of the starting dihydropyridine **24**.

with H_2O. Usual workup gave a brown gum that was purified by chromatography over silica gel, using heptane/EtOAc as eluent (4:1) to give a mixture of adducts (−)-**25** and (+)-**26** (55:45 ratio, 912 mg, 60% yield) as a colorless oil and piperidine diastereoisomers **27** (280 mg, 18% yield). Pure (−)-**25** (208 mg) and (+)-**26** (260 mg) were obtained after chromatography on silica gel using a heptane/AcOEt gradient. Adduct (−)-**25**: $[\alpha]_D$ −129 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.46 (s, 3H), 0.98 (s, 3H), 1.22−1.38 (m, 3H), 1.24 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.2 Hz, 3H), 1.61 (dd, J = 11.5, 2.5 Hz, 1H), 1.72 (s, 1H), 1.82 (m, 1H), 1.92 (m, 1H), 2.16 (d, J = 10.6 Hz, 1H), 2.24 (m, 1H), 2.59 (m, 1H), 2.67 (dd, J = 10.6, 2.5 Hz, 1H), 3.08 (m, 1H), 4.00 (dd, J = 6.6, 6.6 Hz, 1H), 4.01 (dd, J = 6.2, 6.2 Hz, 1H), 7.12−7.33 (m, 10H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ (ppm) 19.5, 22.6, 22.7, 23.9, 26.9, 33.0, 34.8, 38.7 (2C), 39.0, 51.9, 55.7, 57.7, 59.5, 62.3, 63.6, 126.5, 127.0, 127.3, 127.9, 128.3, 129.2 (8C), 145.9, 148.3 (2C); MS (EI) *m/z* (relative intensity) 400 ($M^{+\bullet}$,4), 295 (3), 200 (100), 105 (52); Anal. Calcd for $C_{28}H_{36}N_2$: C, 83.95; H, 9.06; N, 6.99. Found: C, 83.81; H, 8.91; N, 6.85. Adduct (+)-**26**: $[\alpha]_D$ +171 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.97 (s, 3H), 1.03 (m, 1H), 1.07 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.25 (m, 1H), 1.30 (d, J = 6.5 Hz, 3H), 1.31 (m, 1H), 1.50 (dd, J = 10.4, 2.4 Hz, 1H), 1.61 (m, 1H), 1.67 (m, 1H), 2.06 (dd, J = 5.7, 5.7 Hz, 1H), 2.34 (s, 1H), 2.44 (m, 1H), 2.47 (d, J = 10.4 Hz, 1H), 2.64 (dd, J = 6.5, 1.6 Hz, 1H), 2.73 (dd, J = 10.4, 2.4 Hz, 1H), 3.93 (dd, J = 6.5, 6.5 Hz, 1H), 4.00 (dd, J = 6.4, 6.4 Hz, 1H), 7.14−7.37 (m, 10H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm) 19.3, 22.8, 23.3, 23.6 (2C), 26.6, 32.0, 35.2, 39.0, 39.3, 39.5 (2C), 51.7, 54.6, 56.7, 58.3, 61.6, 63.0, 126.5, 127.3, 128.2 (8C), 147.5, 147.7 (2C); MS (EI) *m/z* (relative intensity) 400 ($M^{+\bullet}$,8), 295 (9), 200 (100), 105 (76).

Hydrogenolysis of Adduct (+)-26 To Give Diamine (+)-17. Adduct (+)-**26** (60 mg) was dissolved in a mixture of EtOH (4 mL), EtOAc (4 mL), H_2O (2 mL), and 50% aqueous HBF_4 (2 mL). The resulting homogeneous solution was hydrogenated in a Parr apparatus at 45 psi in the presence of a catalytic amount of 10% palladium on charcoal for 2 days. After filtration over Celite and removal of solvent under reduced pressure, CH_2Cl_2 was added followed by dropwise addition of an aqueous saturated Na_2CO_3 solution until alkaline pH was reached. After removal of solvents under reduced pressure, a 1:1 solution of EtOH/$CHCl_3$ was added, and the resulting solution was stirred overnight at room temperature. Filtration over Celite and removal of solvents under reduced pressure afforded pure diamine (+)-**17** as a colorless oil (24 mg, 89% yield): $[\alpha]_D$ +319 (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.93 (s, 3H), 1.07 (s, 3H), 1.34 (dd, J = 13, 10 Hz, 1H), 1.45 (m, 2H), 1.63 (dd, J = 12, 6 Hz, 1H), 1.73 (m, 1H), 1.87 (dt, J = 13, 10 Hz, 1H), 2.19 (bq, J = 6 Hz, 1H), 2.31 (bs, 1H), 2.63 (d, J = 11 Hz, 1H), 2.74 (dd, J = 7, 1 Hz, 1H), 2.92 (t, J = 5 Hz, 1H), 3.04 (dd, J = 11, 2 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ (ppm) 22.4, 24.7, 24.9, 31.1, 33.6, 35.4, 36.7, 50.3, 51.9, 53.9, 61.7 (2C); MS (ESI) *m/z* (relative intensity) 193 (MH^+, 100).

Supporting Information Available: Full experimental procedures and copies of NMR spectra for compounds **13a**,**b**, **17**, **18a**,**b**, **19b**, **20b**-**21b**, (−)-**25**, (+)-**26**, (±)-**28**, and (±)-**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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