Asymmetric Synthesis of 2-Acetyl-4(5)-(1,2,4-trihydroxybutyl)imidazoles

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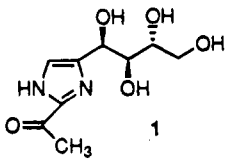
A method for preparing trihydroxybutyl analogues of the biologically active compound 2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI) is reported. This method employs a palladium(0)-catalyzed coupling of 1-(ethoxymethyl)-4-iodoimidazole (**3a**) to functionalized vinylstannane **11**, 1-alkynylstannane **16**, or alkyne **10** to introduce the C-4 imidazole 4-carbon side chain. The 1,2-dihydroxyfunctionality of the butyl side chain was introduced by a Sharpless catalytic asymmetric dihydroxylation.

Introduction

2-Acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (THI, **1**), a constituent of caramel color III, has been found to depress blood lymphocyte counts in both mice and rats.[1]



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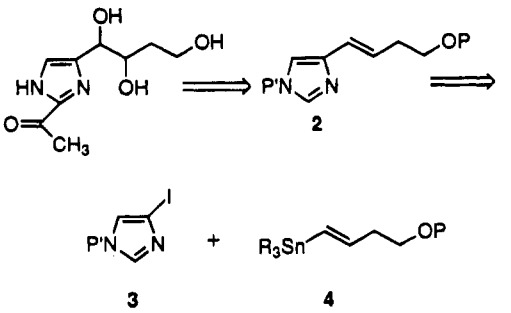
THI produces lymphopenia, apparently without toxic effects, in rats and mice and is able to affect the immune competence in the rat in quite small quantities (e.g., 1–50 ppm in drinking water).[2] THI has also been reported to prevent spontaneous and cyclophosphamide-induced diabetes in nonobese diabetic mice.[3] To investigate the structure–activity relationships of this structurally simple but biologically intriguing molecule we desired a general and flexible synthesis of THI analogues. Three syntheses of THI have been reported, and these all rely on the use of glucose derivatives to prepare the 1,2,3,4-tetrahydroxybutyl side chain.[4–6] These syntheses are either not sufficiently flexible for the synthesis of THI analogues[6] or suffer from poor overall yields.[4,5]

We report here a new synthetic protocol for the synthesis of 1,2,4-trihydroxybutyl THI analogues as outlined in Scheme 1. This involves a palladium-catalyzed coupling of a 1-protected 4-iodoimidazole **3** to a functionalized vinylstannane **4** to produce the alkene **2**, followed by a Sharpless catalytic asymmetric dihydroxylation (AD) to introduce the 1,2-dihydroxy functionality into the butyl side chain (Scheme 1). We chose the ethoxymethyl ($EtOCH_2$-) protecting group for the imidazole nitrogen since this group would assist the introduction of the 2-acetyl group into the imidazole ring later in the synthesis.[7]

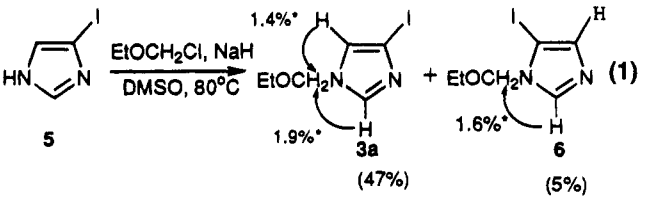
Scheme 1



2 **3** **4**

Results and Discussion

Treatment of 4-iodoimidazole[8] (**5**) with sodium hydride and chloromethyl ethyl ether in DMSO at 80 °C[9] gave a 91:9 mixture of 1-(ethoxymethyl)-4-iodoimidazole (**3a**) and 1-(ethoxymethyl)-5-iodoimidazole (**6**). These isomeric compounds were separated by column chromatography, and their structures were evident from 1D NOE difference experiments (eq 1).[10]



5 **3a** (47%) **6** (5%) [* NOE enhancements]

Heck-type coupling reactions[11,12] between models of **3a** (i.e., 1-*p*-tosyl-4-iodoimidazole (**3b**) or 1-trityl-4-iodoimidazole (**3c**)[8]) and 4-[(*tert*-butyldimethylsilyl)oxy]-1-butene (**7**) failed to give any of alkene **8**. Only 4,4′-biimidazoles **9** were isolated (eq 2).[13]

⊗ Abstract published in *Advance ACS Abstracts,* April 1, 1995.

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(2) Golin, S.J.P.; Phillips, J. A. *Clin. Exp. Immunol.* **1991**, *85*, 335.
(3) Mandel, T. E.; Koulmanda, M.; Mackay, I. R. *Clin. Ext. Immunol.* **1992**, *88*, 414.
(4) Kroplien, U.; Rosdorfer, J.; Vander Geef, J.; Long, R. C., Jr.; Goldstein, J. H. *J. Org. Chem.* **1985**, *50*, 1131.
(5) Sweeny, J. G.; Ricks, E.; Estrada-Valdes, M. C.; Iacobucci, G. A.; Long, R. C., Jr. *J. Org. Chem.* **1985**, *50*, 1133.
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(10) Colombo, R.; Colombo, F.; Derome, A. E.; Jones, J. H.; Rathbone, D. L.; Thomas, D. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1811.
(11) Heck, R. F. *Org. React.* **1982**, *27*, 345. Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: Orlando, 1985.
(12) Heck coupling of 4-iodo-imidazoles has not been previously reported.
(13) 4,4′-Biimidazoles are also isolated in good yield in the absence of the alkene: Cliff, M. D.; Pyne, S. G. *Synthesis* **1994**, 681.

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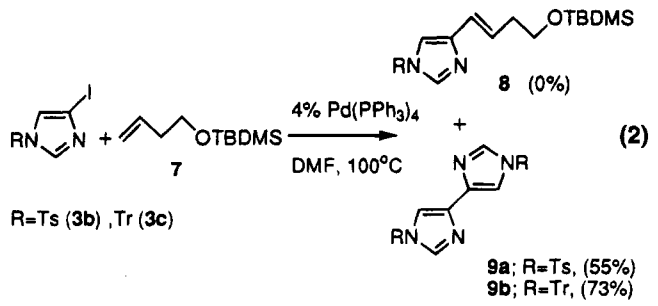


(2)

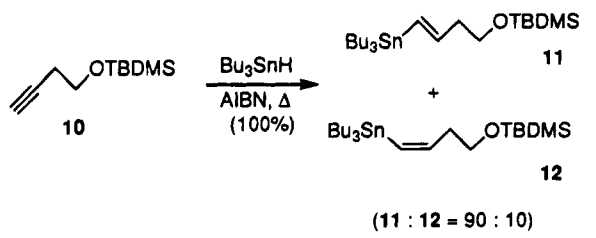
Consequently, Stille-type coupling reactions of **3a** and vinylstannanes were investigated.[14-16] Hydrostannylation[17] of 4-[(*tert*-butyldimethylsilyl)oxy]but-1-yne (**10**) at 120 °C gave an inseparable 90:10 mixture of the (*E*)-and (*Z*)-vinylstannanes **11** and **12** in quantitative yield (Scheme 2). Lower reaction temperatures gave more of the (Z)-isomer.

Treatment of iodoimidazole **3a** with a 81:19 mixture of **11** and **12** (1.05 equiv, prepared from the hydrostannylation of **10** at 80 °C) in the presence of $PdCl_2(PPh_3)_2$[18] (5 mol%) in DMF gave a mixture of the desired alkene adducts **13** and **14** in 5% and 51% yields, respectively (Scheme 3). Treatment of **14** with *n*-butyllithium in THF at −78 °C followed by quenching the resulting 2-lithioimidazole derivative with *N*-methoxy-*N*-methylacetamide[19] (−78 °C to rt) gave the 2-acetylimidazole **15** in 63% yield. Other acetylating agents, for example, acetic anhydride and *N*,*N*-dimethylacetamide, were not effective.

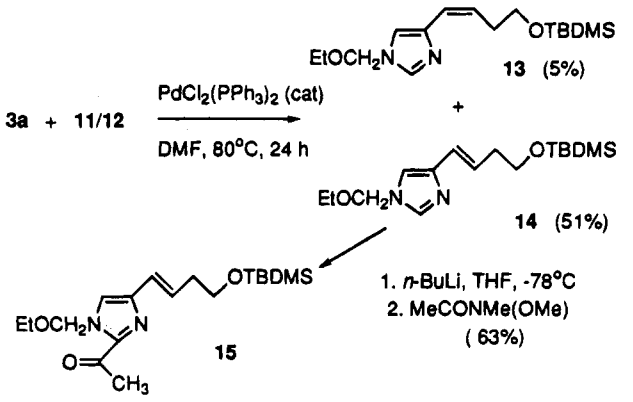
Alternatively the (*Z*)-alkene **13** could be prepared stereoselectively from **3a** in two steps (Scheme 4). The palladium(0)-catalysed coupling of **3a** and **10** (1.5 equiv) in the presence of copper(I) iodide and triethylamine in acetonitrile at reflux[20-22] gave alkyne **17** in 40% yield based on iodoimidazole **3a** and the bialkyne **18** (35% based on **10**), formed from the homocoupling of **10** (Scheme 4). A better yield (59%) of **17** could be realized from the palladium(0)-catalyzed coupling of **3a** and the 1-(trimethylstannyl)alkyne **16** in DMF at 80 °C (Scheme 4).[14,23] The alkyne **17** was converted to the 2-acetyl derivative **19** as described above. Catalytic hydrogenation of **19** over Lindlar's catalyst[24] in the presence of quinoline gave the (*Z*)-alkene **20** in 83% yield.

Asymmetric Dihydroxylations. Catalytic asymmetric dihydroxylation (AD) of **15** at 0 °C for 4 days using

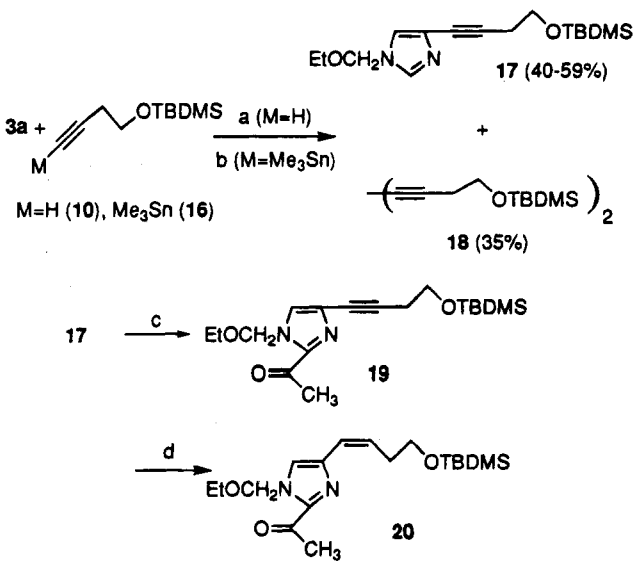
Scheme 2



Scheme 3



Scheme 4[a]

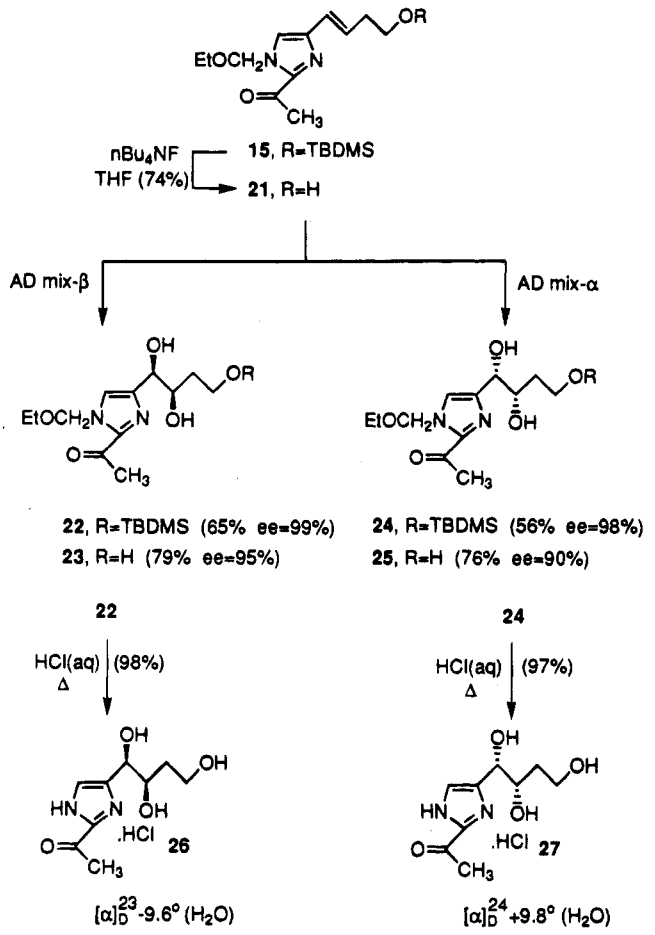


[a] Reaction conditions: (a) 5% $Pd(Ph_3P)_4$, 10% CuI, Et_3N, DMF, 70 °C for **10** (40% yield); (b) 10% $Pd(PPh_3)_4$, DMF, 80 °C, for **16** (59% yield), (c) (1) *n*-BuLi, THF, −78 °C; (2) MeCONMe(OMe) (48%); (d) Lindlar reduction, (83%).

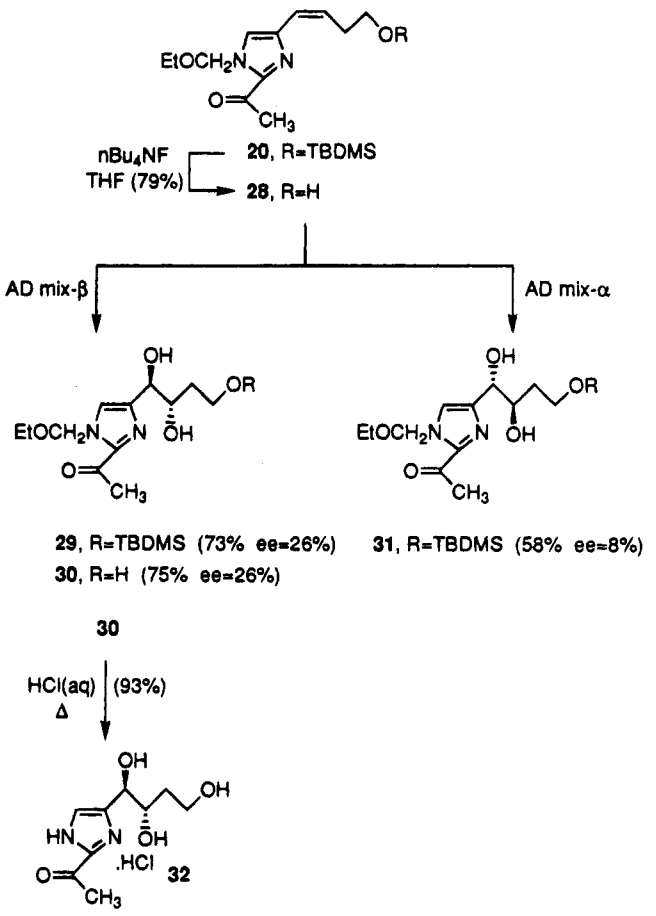
commercially available AD mix-α or AD mix-β[25,26] gave the *syn*-1,2-diols (1′*S*,2′*S*)-**24** or (1′*R*,2′*R*)-**22**, respectively, in moderate yields. The enantiomeric purities of **22** and **24** were 99 and 98%, respectively, as determined by ^1H NMR analysis of their Mosher diesters.[27] Catalytic AD of the alcohol **21** with AD mix-β or AD mix-α gave triols **23** or **25**, respectively, in good yield but in poorer enantiomeric purities as determined by ^1H NMR analysis of their respective tri-Mosher esters (Scheme 5). Hy-

(14) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(15) For a recent review on the palladium-catalyzed coupling reactions of heterocyclic compounds see: Kalinin, V. N. *Synthesis* **1992**, 413.
(16) Stille coupling of 4-iodoimidazole has not been previously reported.
(17) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Ya.L. *Synthesis* **1986**, 496.
(18) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. A.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332.
(19) Prepared according to the general method described in: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(20) In most coupling experiments a number of different coupling conditions were examined to find the optimum reaction conditions; only the optimum conditions are reported. A range of palladium catalysts (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$), solvents (DMF, CH_3CN, and THF), additives (e.g., $AsPh_3$, P(*o*-tol)$_3$), and reaction temperatures were examined.
(21) A significantly higher yield was realized using 1-(benzenesulfonyl)-4-iodoimidazole.
(22) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312.
(23) In model studies, 2-(tributylstannyl)phenylacetylene gave a better coupling yield with **3a** than phenylacetylene itself.
(24) Marvell, E. N.; Thomas, L. *Synthesis* **1973**, 457.
(25) ADmix-α and ADmix-β were purchased from the Aldrich Chemical Co.
(26) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Harting, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.
(27) Dale, J. A.; Dull; D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme 5



Scheme 6



drolysis of **22** and **24** with aqueous hydrochloric acid at reflux for 1 h gave the imidazole hydrochloride salts **26** and **27**, respectively, in excellent yields (Scheme 5). The optical rotations of **26** and **27** were essentially equal and opposite in magnitude.

In contrast to the (*E*)-alkene **15**, the catalytic AD of the (*Z*)-alkene **20** gave the *anti*-1,2-diols **29** and **31** with poor enantiomeric purities (Scheme 6). While the AD of (*Z*)-alkenes is known to give 1,2-diols in lower enantiomeric purities than their isomeric (*E*)-alkenes,[28] it has been reported that higher enantiomeric purities can be realized from (*Z*)-allylic alcohols and (*Z*)-homoallylic alcohols.[29] It has been suggested that hydrogen bonding between the hydroxy group and an oxo group on the osmium is responsible for the higher enantiotropic π-face selectivity in these substrates. However, the AD of homoallylic alcohol **28** gave the 1,2,4-triol **30** in the same enantiomeric purity as that of **29** obtained from the AD of **20**. Acid-catalyzed hydrolysis of **30** gave the imidazole hydrochloride salt **32** in 93% yield. The stereochemical assignments to the products from the AD reactions were based upon Sharpless's mnemonic[26,28] and were supported by ^{1}H NMR analysis of their Mosher esters.[30]

Conclusion

In summary, we have developed a new and potentially general method for the synthesis of THI analogues from 1-(ethoxymethyl)-4-iodoimidazole (**3a**) using palladium(0)-catalyzed coupling reactions with vinylstannanes, alkynes, and 1-(trimethylstannyl)alkynes to prepare 4-alkenyl- and 4-alkynylimidazoles. These methods should be generally useful for preparing other 4-substituted and 2,4-disubstituted imidazoles.[31] The 1-(ethoxymethyl) protecting group allowed regioselective functionalization of the C-2 imidazole position. The catalytic AD was employed to introduce the 1,2-dihydroxy functionality of THI analogues. However, only the (*E*)-alkenes **15** and **21** gave 1,2-diols in high enantiomeric purities. The biological activity of the triols **26**, **27**, and **32** is currently under investigation and will be reported elsewhere.

Experimental Section

All ^{1}H NMR and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively, in $CDCl_3$ solution unless otherwise stated. All organic extracts were dried over $MgSO_4$. Column chromatography was performed on silica gel (70−230 mesh).

1-(Ethoxymethyl)-4(5)-iodoimidazole (3a) and (6). To a solution of 4-iodoimidazole (4.00 g, 20.6 mmol) in DMSO (20 mL) was added NaH (0.540 g, 22.7 mmol), and the solution was stirred at 80 °C under N_2 for 2 h. Chloromethyl ethyl ether (2.34 g, 24.7 mmol) in DMSO (4 mL) was added, and the solution was stirred for a further 2 h at 80 °C. The reaction mixture was then cooled to rt, poured into a 5% aqueous

(28) Sharpless, K. B.; Wang, L. *J. Am. Chem. Soc.* **1992**, *114*, 7568.
(29) Sharpless, K. B.; Van Nieuwenhze, M. S.; *Tetrahedron Lett.* **1994**, *35*, 843.
(30) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(31) The only other generally efficient method for the regioselective preparation of 4-substituted imidazoles employs Grignard and organolithium reagents; see: Turner, R. M.; Ley, S. V.; Lindell, S. D. *Synlett* **1993**, 748.; Ley, S. V.; Lindell, S. D.; Turner, R. M. *J. Chem. Org. Chem.* **1991**, *56*, 5739. Lipshutz, B. H.; Hagen, W. *Tetrahedron Lett.* **1992**, *33*, 5865. Groziak, M. P.; Wei, L. *J. Org. Chem.* **1991**, *56*, 4296. Katritzky, A. R.; Slawinski, J. J.; Brunner, F.; Gorun, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1139.

solution of $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2 (4 × 100 mL). The combined extracts were dried and concentrated to leave a black oil which was purified by short path column chromatography (ethyl acetate/hexane 3/7) to give a mixture of **3a** and **6** as a light yellow oil (2.70 g, 52%). The ratio of **3a** to **6** was 91:9 as determined by ^1H NMR. The two isomers could be separated by careful column chromatography. **3a**: ^1H NMR δ 7.49 (1H, d, J = 1.2 Hz), 7.14 (1H, d, J = 1.2 Hz), 5.24 (2H, s), 3.45 (2H, q, J = 7.2 Hz), 1.19 (3H, t, J = 6.8 Hz); ^{13}C NMR δ 138.6, 124.3, 82.6, 76.2, 64.5, 14.6. MS (ES + ve) m/z 253 (M + H^+, 100), 59 (8); HRMS calcd for $C_6H_9IN_2O$ 251.9760, found 251.9757. **6**: ^1H NMR δ 7.75 (1H, s), 7.15 (1H, s), 5.28 (2H, s), 3.49 (2H, q, J = 7.2 Hz), 1.20 (3H, t, J = 6.8 Hz); ^{13}C NMR δ 140.1, 137.3, 76.3, 69.4, 64.2, 14.6; MS (ES + ve) m/z 253 (M + H^+, 100), 59 (8).

4-Iodo-1-*p*-tosylimidazole (3b). To a stirred solution of 4-iodoimidazole[8] (2.00 g, 10.3 mmol) and *p*-toluenesulfonyl chloride (1.97 g, 10.3 mmol) in dry THF (40 mL) under N_2 was added triethylamine (1.04g, 10.3 mmol) and the solution left to stir for 24 h. The mixture was filtered, and the filtrate was diluted with CH_2Cl_2 (50 mL), washed with water (20 mL), dried, and evaporated. The resulting solid was recrystallized from ethanol to give **3b** as a white solid (2.80 g, 78%): mp 146–147 °C; ^1H NMR δ 7.88 (1H, d, J = 1.2 Hz), 7.83 (2H, d, J = 8.4 Hz), 7.78 (2H, d, J = 8.4 Hz), 7.37 (1H, d, J = 1.2 Hz), 2.46 (3H, s); ^{13}C NMR δ 146.8, 137.6, 134.2, 130.6, 127.5, 122.3, 85.2, 21.8; MS (ES + ve) m/z 349 (M + H^+, 100), 278 (52), 155 (22). Anal. Calcd for $C_{10}H_9IN_2O_2S$: C, 34.50; H, 2.61; N, 8.05. Found: C, 34.95; H, 2.63; N, 8.00.

1,1′-Di-*p*-tosyl-4,4′-biimidazole (9a). In a thick-walled tube was combined 4-iodo-1-tosylimidazole (0.400 g, 1.15 mmol), triethylamine (0.174 g, 1.72 mmol), alkene **7** (0.430 g, 2.30 mmol), and $Pd(Ph_3P)_4$ (53 mg). The reagents were dissolved in dry acetonitrile (4 mL), and the tube was flushed with a stream of nitrogen, sealed, and stirred at 100 °C for 18 h. The solution was filtered, and the filtrate was washed with a 5% aqueous solution of $NaHCO_3$, dried, and concentrated to leave a black solid, which was purified by column chromatography (ethyl acetate/hexane: 45/55) and combined with the solids collected to give **9a** as a cream solid (140mg, 55%), mp 219–220 °C dec. An analytical sample was recrystallized from ethanol: ^1H NMR δ 7.97 (1H, d, J = 1.2 Hz), 7.82 (2H, d, J = 8.8 Hz), 7.60 (1H, d, J = 1.2 Hz), 7.33 (2H, d, J = 8.4 Hz), 2.42 (3H, s); ^{13}C NMR δ 146.4, 138.1, 136.7, 134.7, 130.4, 127.5, 113.4, 21.7; MS (ES + ve) m/z 443 (M + H^+, 100), 279 (27), 102 (57). Anal. Calcd for $C_{20}H_{18}N_4O_4S_2$: C, 54.29; H, 4.10; N, 12.66. Found C, 54.00; H, 4.11; N, 12.51.

1,1′-Ditrityl-4,4′-biimidazole (9b). In a thick-walled tube was combined 4-iodo-1-tritylimidazole[8] (1.02 g, 2.30 mmol), alkene **7** (860 mg, 4.60 mmol), triethylamine (4.60 mmol), and $Pd(Ph_3P)_4$ (100 mg). Dry DMF (5 mL) was added, the tube was flushed with N_2 and sealed, and the contents were stirred at 100 °C for 24 h. The mixture was filtered, and the filtrate was added to a 5% aqueous solution of $NaHCO_3$ (10 mL) and refiltered. The combined solids were washed with water and then acetone to give a cream solid which was recrystallized from $CHCl_3$/toluene (1/1) to give **9b** as a white solid (0.52 g, 73%), mp 279–280 °C dec. Extraction of the aqueous phase with CH_2Cl_2 gave no identifiable olefinated product **8**: ^1H NMR δ 7.36 (1H, d, J = 1.6 Hz), 7.32–7.29 (9H, m), 7.28 (1H, d, J = 1.6 Hz), 7.19–7.17 (6H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$, in part) δ 142.7, 138.9, 136.7, 129.9, 128.0, 127.9, 117.1; MS (ES + ve) m/z 619.0 (M + H^+, 61), 241 (100); HRMS calcd for $C_{44}H_{34}N_4$ 618.2783, found 618.2778.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-(tributylstannyl)-*trans*-1-butene (11). A mixture of the alkyne **10** (2.20 g, 12.0 mmol) and a catalytic amount of AIBN under N_2 was stirred at 80 °C. Tributyltin hydride (3.16 g, 10.9 mmol) was added, and the reaction was stirred at 80 °C for 3 h. The mixture was cooled to rt, and excess **10** was removed under high vacuum to give a quantitative yield (5.17 g) of a mixture of the stannanes **11** and **12** as a clear oil (**11**:**12** = 81:19). No attempts were made to separate this mixture which was used in the next step without further purification. **11**: ^1H NMR δ 5.97–5.95 (2H, m, $J_{Sn,H}$ = 77.6 Hz), 3.67 (2H, t, J = 6.8 Hz), 2.36 (2H, ddt, J = 2.0, 3.2, 6.8 Hz), 1.52–1.25 (18H, m), 0.90–0.85 (18H, m). **12:** ^1H NMR δ 6.51 (1H, dt, J = 6.8, 12.8 Hz), 5.89 (1H, dt, J = 1.2, 12.4 Hz), 3.64 (2H, t, J = 7.2 Hz), 2.27 (2H, dq, J = 1.2, 6.8 Hz), 1.52–1.25 (18 H, m), 0.90–0.85 (18H, m), 0.06 (6H, s).

4-[4-[(*tert*-Butyldimethylsilyl)oxy]*trans*-1-butenyl]-1-(ethoxymethyl)imidazole (14). A mixture of iodoimidazole **3a** (2.63 g, 10.4 mmol), vinylstannanes **11** and **12** (5.17 g, 10.9 mmol, 81:19 trans/cis isomers), and $PdCl_2(Ph_3P)_2$ (370 mg) in a thick-walled tube was dissolved in dry DMF (30 mL). The vessel was flushed with argon and sealed and then stirred in the dark at 80 °C for 24 h. The mixture was then cooled and diluted with ethyl acetate (200 mL). The solution was washed with a half-saturated aqueous solution of NaCl (3 × 80 mL), dried, and concentrated to leave a dark oil. Purification by column chromatography (ethyl acetate/hexane: 4/6) gave pure *cis*-**13** (0.145 g, 5%) and pure *trans*-**14** (1.64 g, 51%) as yellow oils. **13**: ^1H NMR δ 7.56 (1H, s), 7.06 (1H, s), 6.38 (1H, dt, J = 1.6, 11.6 Hz), 5.64 (1H, dt, J = 7.2, 12.0 Hz), 5.26 (2H, s), 3.76 (2H, t, J = 6.8 Hz), 3.46 (2H, q, J = 7.2 Hz), 2.67 (2H, dq, J = 1.6, 6.8 Hz), 1.19 (3H, t, J = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR δ 140.4, 136.6, 127.1, 122.5, 117.2, 76.2, 64.3, 62.6, 32.9, 25.9, 18.3, 14.7, −5.3; MS (CI + ve) m/z 311 (M + H^+, 48), 295 (11), 253 (100), 197 (71), 179 (38), 166(46). **14**: ^1H NMR δ 7.51 (1H, d, J = 1.2 Hz), 6.90 (1H, d, J = 1.6 Hz), 6.33–6.31 (2H, m), 5.22 (2H, s), 3.71 (2H, t, J = 7.2 Hz), 3.43 (2H, q, J = 6.8 Hz), 2.42–2.37 (2H, m), 1.18 (3H, t, J = 6.8 Hz), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR δ 141.1, 137.1, 126.1, 123.0, 115.1, 76.2, 64.2, 63.0, 36.5, 25.9, 18.3, 14.6, −5.3; MS (ES + ve) m/z 311 (M + H^+, 100), 288 (14); HRMS calcd for $C_{16}H_{30}N_2O_2Si$ 310.2076, found 310.2091.

2-Acetyl-4-[4-[(*tert*-butyldimethylsilyl)oxy]-*trans*-1-butenyl]-1-(ethoxymethyl)imidazole (15). Alkene **14** (2.00 g, 6.45 mmol) was dissolved in dry THF (10 mL) and set to stir under N_2 at −78 °C. *n*-BuLi (7.74 mmol) in hexanes was added, and the black solution was stirred for 1 h at −78 °C. Freshly distilled *N*-methoxy-*N*-methylacetamide[19] (930 mg, 9.03 mmol) in dry THF (5 mL) was then added slowly, and the resulting solution was stirred for 1 h at −78 °C and for a further 1 h at rt. The mixture was diluted with CH_2Cl_2 (40 mL), washed with a 5% aqueous solution of $NaHCO_3$ (15 mL), dried, and concentrated to give a black oil. Purification of this oil by column chromatography (ethyl acetate/hexane: 4/6) gave **15** as a tan oil (1.43 g, 63%, 80% based on recovered alkene **14**) and starting alkene **14** (0.42 g): ^1H NMR δ 7.19 (1H, s), 6.44–6.33 (2H, m), 5.75 (2H, s), 3.74 (2H, t, J = 7.2 Hz), 3.53 (2H, q, J = 6.8 Hz), 2.67 (3H, s), 2.46–2.41 (2H, m), 1.19 (3H, t, J = 7.2 Hz), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR δ 190.0, 142.3, 140.7, 128.1, 122.7, 120.9, 77.0 ($EtOCH_2$, over $CDCl_3$), 64.8, 62.8, 36.4, 27.3, 25.9, 18.3, 14.8, −5.3; MS (CI + ve) 353 (M + H^+, 13), 337 (6), 307 (15), 295 (65), 207(22); HRMS calcd for $C_{18}H_{32}N_2O_3Si$ 353.2182, found 352.2177.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-(trimethylstannyl)-1-butyne (16). Butyne **10** (3.00g, 16.30 mmol) was dissolved in dry THF (10 mL), cooled to −78 °C, and set stirring under N_2. *n*-BuLi in hexanes (17.93 mmol) was then added, and the reaction was stirred for 10 min at −78 °C and 20 min at 0 °C. Trimethyltin chloride (3.40 g, 19.56 mmol) in THF (5 mL) was then added dropwise with LiCl precipitating out immediately. The mixture was then left to stir at 0 °C for 30 min and overnight at rt. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with H_2O (15 mL) and then a saturated aqueous solution of NaCl (15 mL). The solution was dried and the solvent removed to leave a light yellow oil. Short path distillation (65 °C/0.5 mmHg) gave stannane **16** as a clear oil (4.84g, 86%): ^1H NMR δ 3.72 (2H, t, J = 7.2 Hz), 2.45 (2H, t, J = 7.2 Hz), 0.893 (9H, s), 0.26 (9H, s, $^2J_{119Sn,H}$ = 60.4 Hz, $^2J_{117Sn,H}$ = 58.0 Hz), 0.07 (6H, s); HRMS calcd for $C_{13}H_{29}Si^{120}SnO$ 349.1011, found 349.1011.

4[4-[(*tert*-Butyldimethylsilyl)oxy]-1-butynyl]-1-(ethoxymethyl)imidazole (17). Method a. A mixture of iodoimidazole **3a** (0.500 g, 1.98 mmol), alkyne **10** (0.550 g, 2.98 mmol), triethylamine (2.00 g, 19.8 mmol), CuI (40 mg), and $PdCl_2(Ph_3P)_2$ (70 mg) were dissolved in dry acetonitrile (10 mL). The solution was degassed with argon and heated to reflux under N_2 for 3 h. The solution was cooled to rt, poured

into H_2O (80 mL), and extracted with CH_2Cl_2 (3 × 100 mL), and the extracts were dried. The solvent was removed to leave a red oil which was purified by column chromatography (ethyl acetate/hexane: 55/45) to give pure **17** (242 mg, 40% based on **3a**) and 1,8-bis[(*tert*-butylbismethylsilyl)oxy]-3,5-octadiyne (**18**) as a dark oil (380 mg, 35% from **10**).

Method b. Into a thick-walled tube was added iodoimidazole **3a** (0.50 g, 1.98 mmol), stannane **16** (1.03 g, 2.97 mmol), and $Pd(Ph_3P)_4$ (229 mg). The reagents were dissolved in dry DMF (8 mL), and the vessel was flushed with argon, sealed, and left to stir for 24 h at 80 °C. The dark mixture was then diluted with ethyl acetate (40 mL), filtered, washed with H_2O (2 × 15 mL), dried, and concentrated to give a dark oil. Purification by column chromatography (ethyl acetate/hexane: 1/1) gave **17** (360 mg, 59%): ^{1}H NMR δ 7.50 (1H, d, J = 1.2 Hz), 7.13 (1H, d, J = 1.2 Hz), 5.23 (2H, s), 3.81 (2H, t, J = 7.6 Hz), 3.43 (2H, q, J = 7.2 Hz), 2.62 (2H, t, J = 7.6 Hz), 1.18 (3H, t, J = 6.8 Hz), 0.90 (9H, s), 0.08 (6H, s); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 136.9, 125.5, 121.6, 86.9, 76.3, 74.8, 64.6, 61.8, 25.8, 23.7, 18.2, 14.5, −5.4; MS (ES + ve) *m/z* 309 (M + H$^+$, 100); HRMS calcd for $C_{15}H_{25}N_2O_2Si$ (M$^+$ − Me) 293.1685, found 293.1676.

1,8-Bis[(*tert*-butyldimethylsilyl)oxy]-3,5-octadiyne (18). An analytical sample of **18** was obtained as a pale oil after distillation (Kugelrohr, 117 °C/0.5 mmHg): ^{1}H NMR δ 3.72 (4H, t, J = 7.2 Hz), 2.46 (4H, t, J = 7.2 Hz), 0.89 (18H, s), 0.07 (12H, s); ^{13}C NMR δ 74.5, 66.3, 61.5, 25.8, 23.6, 18.3, −5.4; MS (ES + ve) *m/z* 367 (M + H$^+$, 100), 309 (74); HRMS calcd for $C_{19}H_{24}O_2Si_2$ 351.2175, found 351.2174.

2-Acetyl-4-[4-[(*tert*-butyldimethylsilyl)oxy]-1-butynyl]-1-(ethoxymethyl)imidazole (19). Imidazole **17** (400 mg, 1.30 mmol) was dissolved in dry THF (4 mL) and was stirred under N_2 at −78 °C. *n*-BuLi in hexanes (2.73 mmol) was added, and the reaction was stirred for 1 h at −78 °C before *N*-dimethoxy-*N*-methylacetamide (0.350 g, 3.25 mmol) was added dropwise in THF (5 mL). The mixture was then stirred for 1 h at −78 °C and a further 1 h at rt before being diluted with CH_2Cl_2 (15 mL). The solution was washed with a 5% aqueous solution of $NaHCO_3$ (6 mL), and the dark solution was dried. The solvent was removed, and purification by column chromatography (ethyl acetate/hexane: 1/9) gave **19** (220 mg, 48%) as a tan oil: ^{1}H NMR δ 7.35 (1H, s), 5.75 (2H, s), 3.82 (2H, t, J = 7.2 Hz), 3.53 (2H, *q*, J = 7.2 Hz), 2.67 (3H, s), 2.64 (2H, t, J = 7.2 Hz), 1.20 (3H, t, J = 7.2 Hz), 0.91 (9H, s), 0.09 (6H, s); ^{13}C NMR δ 190.4, 141.9, 127.0, 124.9, 87.8, 77.3, 73.9, 65.0, 61.5, 27.3, 25.8, 23.6, 18.2, 14.7, −5.4; MS (ES + ve) *m/z* 351 (M + H$^+$, 100), 317 (6), 289 (16); IR (neat) 2247, 1683 cm^{-1}; HRMS calcd for $C_{17}H_{29}N_2O_3Si$ 335.1791, found 335.1758.

2-Acetyl-4-[4-[(*tert*-butyldimethylsilyl)oxy]-*cis*-1-butenyl]-1-(ethoxymethyl)imidazole (20). A solution of acetylimidazole **19** (1.00 g, 2.86 mmol), quinoline (370 mg, 2.86 mmol), and 10% $Pd/CaCO_3$ (160 mg) in ethyl acetate/hexane (15 mL, 1:1) was stirred under a H_2 atmosphere (1 atm) for 90 min. The mixture was then filtered and concentrated in vacuo, and the crude product was purified by column chromatography (ethyl acetate/hexane: 2/98) to give the *cis*-alkene **20** (840 mg, 83%): ^{1}H NMR δ 7.30 (1H, s), 6.37 (1H, dt, J = 11.6, 1.6 Hz), 5.77 (2H, s), 5.75 (1H, dt, J = 11.6, 7.2 Hz), 3.77 (2H, t, J = 6.8 Hz), 3.54 (2H, q, J = 6.8 Hz), 2.73 (2H, dq, J = 2.0, 6.8 Hz), 2.67 (3H, s), 1.20 (3H, t, J = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR δ 191.0, 142.0, 139.9, 129.4, 123.4, 121.7, 77.0, 64.9, 62.6, 32.9, 27.4, 25.9, 18.3, 14.9, −5.3; MS (ES + ve) *m/z* 353 (M + H$^+$, 100), 316 (20), 288 (55); IR (neat) 1680 cm^{-1}; HRMS calcd for $C_{17}H_{29}N_2O_3Si$ (M$^+$ − Me) 337.1947, found 337.1933.

2-Acetyl-4-(4-hydroxy-*trans*-1-butenyl)-1-(ethoxymethyl)imidazole (21). Silyl ether **15** (700 mg, 1.99 mmol) and Bu_4NF (1.04 g, 3.98 mmol) were dissolved in THF (10 mL), and the solution was stirred at rt for 75 min. The dark solution was then diluted with ethyl acetate (30 mL) and washed consecutively with a saturated aqueous solution of NaCl (10 mL) and H_2O (10 mL). The aqueous washings were extracted with ethyl acetate (2 × 20 mL), and the combined extracts were dried and concentrated to leave a thick dark oil. Purification by column chromatography (ethyl acetate/hexane: 1/1) gave a light yellow oil which solidified on standing (350 mg, 74%): mp 80−81 °C; ^{1}H NMR δ 7.20 (1H, s), 6.43−6.41 (2H, m), 5.75 (2H, s), 3.80−3.75 (2H, m), 3.53 (2H, q, J = 7.2 Hz), 2.68 (3H, s), 2.51−2.67 (2H, m), 1.59 (1H, t, J = 5.6 Hz), 1.19 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 191.0, 142.3, 140.4, 127.6, 123.7, 121.3, 77.1, 64.9, 61.8, 36.2, 27.4, 14.8. MS (ES + ve) *m/z* 239 (M + H, 100), 197 (15). Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.66; H, 7.82; N, 11.58.

(1*R*,2*R*)-2-Acetyl-4-[1,2-dihydroxy-4-(*tert*-butyldimethylsiloxy)butyl]-1-(ethoxymethyl)imidazole (22). Representative AD Procedure. To a stirred solution of AD mix-β (1.80 g) and $(DHQD)_2PHAL$ (40 mg) in H_2O (6.5 mL) and t-BuOH (3 mL) at rt was added methanesulfonamide (244 mg, 2.56 mmol). The two-phase system was then cooled to 0 °C, and the *trans*-alkene **21** (400 mg, 1.14 mmol) in t-BuOH (3.5 mL) was added in one addition. The system was left to stir at 0 °C for 3 d. Na_2SO_3 (1.8 g) was then added at 0 °C, and the mixture was warmed to rt and left to stir for 1 h. H_2O (2 mL) was added, the mixture was extracted with CH_2Cl_2 (4 × 10 mL) and dried, and the solvent was removed to leave a yellow oil. Purification by column chromatography (ethyl acetate/hexane: 4/6) gave a thick yellow syrup (285 mg, 65%): $[\alpha]_D^{25}$ −13.7° (*c* 2.85, $CHCl_3$); ee = 99%; ^{1}H NMR δ 7.33 (1H, s), 5.75 (2H, ABq, J = 10.8 Hz), 4.61 (1H, dd, J = 4.0, 5.6 Hz), 4.16 (1H, dt, J = 4.0, 7.2 Hz), 4.01 (1H, d, J = 3.2 Hz), 3.91−3.88 (2H, m), 3.55 (2H, q, J = 6.8 Hz), 3.50 (1H, d, J = 6.4 Hz), 2.64 (3H, d, J = 0.4 Hz), 1.91−1.78 (2H, m), 1.20 (3H, t, J = 6.8 Hz), 0.91 (9H, s), 0.10, 0.09 (2 × 3H, 2 × s); ^{13}C NMR δ 190.5, 143.3, 141.8, 122.2, 77.02, 73.0, 70.8, 64.9, 61.0, 35.0, 27.2, 25.7, 18.0, 14.7, −5.65, −5.67; MS (CI + ve) *m/z* 387 (M + H$^+$, 100), 371 (12), 329 (10); HRMS calcd for $C_{18}H_{35}N_2O_5Si$ 387.2315, found 387.2326.

(1*R*,2*R*)-2-Acetyl-4-(1,2,4-trihydroxybutyl)-1-(ethoxymethyl)imidazole (23). Using the general procedure described above for the synthesis of **22**, compound **23** was obtained as a white solid (79%), after purification by column chromatography (methanol/ethyl acetate: 1/9): mp 102−103 °C; $[\alpha]_D^{26}$ −11.2° (*c* 1.35, MeOH); ee = 95%; ^{1}H NMR δ 7.31 (1H, s), 5.77, 5.74 (2H, ABq, J = 10.4 Hz), 4.54 (1H, dd, J = 4.0, 7.2 Hz), 4.21−4.16 (1H, m), 3.92−3.89 (2H, m), 3.92−3.89 (2H, m), 3.87 (1H, d, J = 2.8 Hz), 3.56 (2H, q, J = 6.8 Hz), 3.50 (1H, d, J = 5.2 Hz), 3.10−3.08 (1H, m), 2.64 (3H, s), 2.01−1.92 (1H, m), 1.84−1.77 (1H, m), 1.21 (3H, t, J = 6.8 Hz); ^{13}C NMR (CD_3OD) δ 191.5, 144.8, 143.0, 124.7, 78.1, 72.7, 65.8, 60.0, 36.7, 27.4, 15.2; MS (CI + ve) *m/z* 256 (M$^+$ − CH_3, 13), 237 (26), 209 (26), 97 (64), 139 (100). Anal. Calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.65; H, 7.53; N, 10.02.

(1*S*,2*S*)-2-Acetyl-4-[1,2-dihydroxy-4-[(*tert*-butyldimethylsilyl)oxy]butyl]-1-(ethoxymethyl)imidazole (24). Using the general procedure described above for the synthesis of **22**, compound **24** was obtained as a thick yellow syrup (56%) after purification by column chromatography (ethyl acetate/hexane: 4/6): $[\alpha]_D^{25}$ 13.3° (*c* 2.45, $CHCl_3$); ee = 98%. Spectral data were identical to **22**.

(1*S*,2*S*)-2-Acetyl-4-(1,2,4-trihydroxybutyl)-1-(ethoxymethyl)imidazole (25). Using the general procedure described above for the synthesis of **22**, compound **25** was obtained as a white solid (76%), mp 102−103 °C, after purification by column chromatography (methanol/ethyl acetate: 1/9): $[\alpha]_D^{26}$ 11.7° (*c* 1.3, MeOH); ee = 90%. Spectral data were identical to **23**.

(1*R*,2*R*)-2-Acetyl-4-(1,2,4-trihydroxybutyl)imidazolium Chloride (26). Representative Deprotection Procedure. A solution of the silyl ether **22** (280 mg, 0.73 mmol) in ethanol/H_2O (1:1, 10 mL) and concd HCl (5 mL) was refluxed for 1 h and cooled to rt, and the ethanol removed in vacuo. The aqueous solution was washed with ether (3 × 5 mL) and concentrated to give the HCl salt **26** as a tan solid (180 mg, 98%): mp 236-242 °C dec; $[\alpha]_D^{23}$ −9.6° (*c* 1.80, H_2O); ^{1}H NMR (D_2O) δ 7.46 (1H, s), 4.73 (1H, d, J = 4.4 Hz), 3.84 (1H, dd, J = 4.0, 14 Hz), 3.57−3.52 (2H, m), 2.53 (3H, s), 1.64−1.46 (2H, m); ^{13}C NMR (D_2O, MeOH internal reference) δ 184.7, 139.4, 137.0, 119.3, 70.1, 68.3, 58.2, 34.2, 26.4; MS (ES + ve) *m/z*

215 ($C_9H_{15}N_2O_4^+$, 100), 197 (15); HRMS calcd for $C_9H_{15}N_2O_4$ 215.1032, found 215.1043.

(1*S*,2*S*)-2-Acetyl-4-(1,2,4-trihydroxybutyl)imidazolium Chloride (27). Using the general procedure described above for the synthesis of **26**, compound **27** was obtained as a tan solid (97%), $[\alpha]_D^{24}$ +9.8° (*c* 1.50, H_2O). Spectral data were identical to **26**.

2-Acetyl-4-(4-hydroxy-*cis*-1-butenyl)-1-(ethoxymethyl)imidazole (28). Silyl ether **20** (0.750 g, 2.13 mmol) and Bu_4NF (1.11 g, 4.26 mmol) were dissolved in THF (10 mL) and stirred at rt for 75 min. The solution was diluted with ethyl acetate (30 mL) and washed consectuviely with a saturated aqueous solution of NaCl (10 mL) and H_2O (10 mL). The aqueous phase was re-extracted with ethyl acetate (20 mL), and the combined extracts were dried and concentrated to leave a thick oil. Purification by column chromatography (ethyl acetate/hexane: 35/65) gave alcohol **28** as a yellow oil (400mg, 79%): ^1H NMR δ 7.24 (1H, s), 6.45 (1H, d, J = 11.6 Hz), 5.88–5.80 (1H, m), 5.77 (2H, s), 4.34 (1H, br s), 3.89–3.84 (2H, m), 3.56 (2H, q, J = 7.2 Hz), 2.81–2.75 (2H, m), 2.67 (3H, s), 1.21 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 190.3, 141.3, 139.1, 129.9, 123.3, 121.8, 76.95, 64.9, 61.9, 31.8, 27.3, 14.6; MS (ES + ve) *m/z* 239 (M + H^+, 100), 197 (18), 102 (9), 59 (17); HRMS calcd for $C_{12}H_{18}N_2O_3$ 238.1317, found 238.1315.

(1*R*,2*S*)-2-Acetyl-4-[1,2-dihydroxy-4-(*tert*-butyldimethylsiloxy)butyl]-1-(ethoxymethyl)imidazole (29). Using the general procedure described above for the synthesis of **22**, compound **29** was obtained as a light yellow oil (73%) after purification by column chromatography (ethyl acetate/hexane: 35/65): ee = 26%; ^1H NMR δ 7.34 (1H, s), 5.75 (2H, s), 4.64 (1H, t, J = 5.2 Hz), 4.32 (1H, d, J = 2.8 Hz), 4.05–4.00 (1H, m), 3.94 – 3.84 (2H, m), 3.74 (1H, d, J = 4.8 Hz), 3.55 (2H, q, J = 7.2 Hz), 2.63 (3H, s), 1.86–1.81 (2H, m), 1.20 (3H, t, J = 7.2 Hz), 0.91 (9H, s), 0.10 (6H, s); ^{13}C NMR δ 190.5, 143.4, 141.7, 122.2, 77.2, 74.4, 70.8, 65.0, 61.2, 34.6, 27.3, 25.8, 18.1, 14.8, –5.5; MS (ES + ve) *m/z* 387 (M + H^+, 100), 332 (7); HRMS calcd for $C_{18}H_{35}N_2O_5Si$ 387.2314, found 387.2307.

(1*R*,2*S*)-2-Acetyl-4-(1,2,4-trihydroxybutyl)-1-(ethoxymethyl)imidazole (30). Using the general procedure described above for the synthesis of **22**, compound **30** was obtained as a white solid (75%), after purification by column chromatography (methanol/ethyl acetate: 1/9); mp 83–84 °C; ee = 26%; ^1H NMR δ 7.34 (1H, s), 5.76 (2H, s), 4.65 (1H, d, J = 5.6 Hz), 4.12–4.04 (1H, m), 3.96–3.86 (2H, m), 3.56 (2H, q, J = 7.2 Hz), 2.64 (3H, s), 1.87–1.74 (2H, m), 1.21 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 190.2, 142.8, 141.7, 122.6, 77.1, 73.5, 71.0, 65.1, 59.8, 34.0, 27.2, 14.7; MS (ES + ve) *m/z* 294 (M + Na^+, 100), 139 (100), 102 (65).

(1*S*,2*R*)-2-Acetyl-4-[1,2-dihydroxy-4-[(*tert*-butyldimethylsilyl)oxy]butyl]-1-(ethoxymethyl)imidazole (31). Using the general procedure described above for the synthesis of **22**, compound **31** was obtained as a thick pale oil (58%), after purification by column chromatography (ethyl acetate/hexane: 35/65), ee = 8%. Spectral data were identical to **29**.

(1*R*,2*S*)-2-Acetyl-4-(1,2,4-trihydroxybutyl)imidazolium Chloride (32). Triol **30** (110mg, 0.40 mmol) was dissolved in ethanol/H_2O (1:1, 8 mL) and concd HCl (4 mL), and the solution was heated to reflux for 1 h. The solvent was then removed and the sample dried under high vacuum at ca. 60 °C for 2 h to give a highly hydroscopic yellow glassy solid of the HCl salt **32** (94mg, 93%). An analytical sample was recrystallized from ethanol/acetonitrile: mp 129–131 °C; ^1H NMR (D_2O/DCl) δ 7.56 (1H, s), 4.78 (1H, d, J = 5.2 Hz), 3.96 (1H, ddd, J = 2.8, 5.6, 10.0 Hz), 3.67–3.63 (2H, m), 2.63 (s, 3H), 1.82–1.70 (1H, m), 1.49–1.40 (1H, m); ^{13}C NMR (D_2O/DCl, MeOH reference) δ 185.2, 139.8, 136.7, 119.8, 70.4, 68.9, 58.2, 34.4, 26.3; MS (ES + ve) *m/z* 215 (M + H^+, 100), 197 (59), 179 (47). Anal. Calcd for $C_9H_{15}ClN_2O_4.1/3H_2O$: C, 42.17; H, 6.15; N, 10.91. Found: C, 42.32; H, 6.18; N, 10.61.

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Supplementary Material Available: ^1H NMR of *N*-methyl-*N*-methoxyacetamide, **3b**, **9b**, **11** (and **12**), **13–23**, **29**, **30**, and **32**. ^{13}C NMR of **5**, **6**, **9a**, and **26** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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