An Approach to the Cyclopeptide Alkaloids (Phencyclopeptines) via Heterocyclic Diamide/Dipeptide Equivalents. Preparation and N-Alkylation Studies of 2,4(5)-Disubstituted Imidazoles

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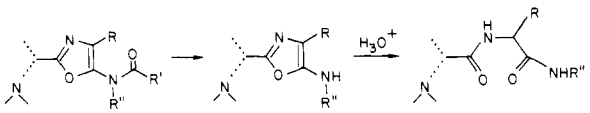
2,4(5)-Disubstituted imidazoles containing a variety of substituents have been prepared via a modified literature procedure. An extensive study regarding the site of N-alkylation is reported which demonstrates that a strong preference exists for 1,2,4-trisubstituted products with little or no formation of the corresponding 1,2,5-trisubstituted isomers. The relationship of imidazoles with this substitution pattern to the phencyclopeptines is disclosed in preliminary studies by virtue of their unmasking to diamides/dipeptides under the influence of singlet molecular oxygen.

We have recently described the preparation and alkylation chemistry of 2,4-disubstituted 5-(acylamino)oxazoles 1 and their potential role as diamide/dipeptide equivalents



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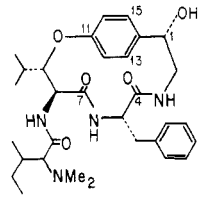
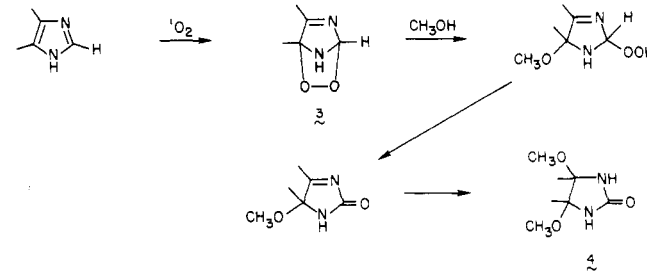
en route to the naturally occurring cyclopeptide alkaloids.[2,3] These bases, typified by pandamine (2), the first member



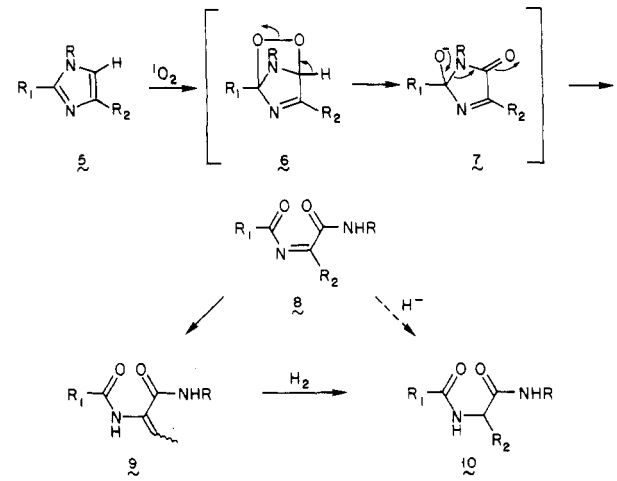
2, Pandamine

of this class of natural products to be fully characterized in 1966 by Pais and co-workers,[4] are of current interest as they apparently display ionophoric activity.[5,6] While the appropriately substituted oxazoles represent one approach to this ring system, other heterocyclic ring systems were envisioned as serving in a similar capacity. In this paper we describe the preparation of a number of new 2,4(5)-disubstituted imidazoles via an improved procedure, which, upon treatment with base and an alkylating agent, are converted to their trisubstituted derivatives. To our knowledge, this is the first such general study on the regiochemistry of N-alkylation of imidazoles of this type. This was most surprising in view of the extensive role that imidazoles in general play in many biological processes. In addition, preliminary studies on the unmasking of a

Scheme I



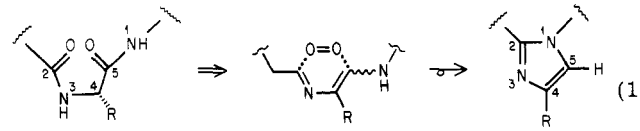
Scheme II



1,2,4-trisubstituted imidazole to its diamide and potential dipeptide equivalent is presented in terms of a hetercyclophane route to the phencyclopeptines.

Background

Inspection of the requirements for a diamide, the key structural feature of the macrocyclic ring itself, suggested that the 1,6 arrangement of oxygen atoms might be arrived at via a [4 + 2]-cycloaddition process involving an azabutadiene backbone illustrated in eq 1. Clearly, if N_1 is



(1)

bonded to carbon 2, this forms an imidazole ring that requires the addition of singlet molecular oxygen across the 2,5-positions. The majority of known singlet oxygen

(1) Recipient of an American Cancer Society Junior Faculty Research Award, 1981–1983.

(2) Lipshutz, B. H.; Hungate, R. W.; McCarthy, K. M. *J. Am. Chem. Soc.*, in press.

(3) For general reviews on the phencyclopeptines, see: (a) Bycroft, B. W.; Wels, C. M. *Amino-Acids, Pept., Proteins*, **1976**, *8*, 310. (b) Tschesche, R.; Kauszman, E. U. *Alkaloids* **1955**, *15*, 165. (c) Pais, M.; Jarreau, F.-X. In "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins"; Weinstein, B., Ed.; Marcel Dekker: New York, 1971; Vol. 1, p 127. (d) Warnhoff, E. W. *Alkaloids (London)* **1971**, *1*, 444.

(4) Pais, M.; Jarreau, F.-X.; Lusinchi, X.; Goutarel, R. *Ann. Chim. (Paris)* **1966**, *13*, 83 and references therein.

(5) Kawai, K.; Nozawa, Y.; Ogihara, Y. *Experientia* **1977**, *33*, 1454.

(6) Goff, D.; Lagarias, J. C.; Shih, W. C.; Klein, M. P.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4814. Lagarias, J. C.; Houghton, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202.

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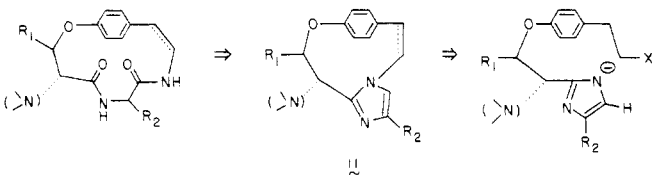
Scheme III

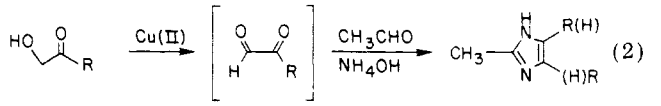


chemistry of imidazoles has been elucidated by Wasserman and co-workers,[7] where a similar sequence of events on a 2-protioimidazole is shown in Scheme I. Compound **4** does not, of course, resemble a diamide, let alone a dipeptide; yet we hypothesized that products of this type result from the fact that a protic, nucleophilic medium (i.e., MeOH) had been selected which invariably participated in the reaction. Switching to a dry, nonnucleophilic solvent should encourage second-stage breakdown of intermediate endoperoxide **3**, perhaps with the aid of a suitable base, according to Scheme II.

Diels–Alder-like addition of $^1O_2$ to **5** would form initially endoperoxide **6**, which bears a labile proton at the 5-position. α-Elimination breaks the weak peroxide bond, giving amide hemiaminal **7**, which would open up to diamide **8**. Intermediate **8** would be expected to tautomerize to enamine **9** should R_2 contain a carbon-bearing proton at the α-position to the imine. Alternatively, without a proton available, mild hydride reduction should afford diamide **10**. Furthermore, with R_1 = CH(NR′R″)R_4, **8** represents a precursor to the corresponding dipeptides. Hence, ultimately the proposal for entry to the cyclopeptide alkaloids translates into the preparation of a mixed heterocyclophane **11**, as illustrated retrosynthetically in Scheme III. The realization of this sequence, assuming the conversion of **5** to **10** proceeds as planned, would ultimately depend upon cyclization via N-alkylation resulting in a 1,2,4- (vs. a 1,2,5-)trisubstituted imidazolophane (i.e., **11**).

Preparation of 2,4(5)-Disubstituted Imidazoles

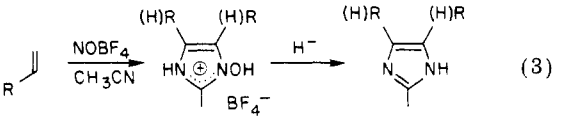
According to our proposal outlined in Scheme II for converting imidazoles to diamides/dipeptides, the substituent at the 4-position is to correspond to a fragment of a masked amino acid (e.g., R = $(CH_3)_2CHCH_2$ → leucine). Thus, a general approach to 2,4(5)-disubstituted systems was needed that allowed incorporation of these specific appendages. While numerous methods for imidazole formation with substitution patterns of this type can be found in the literature,[8,9] very few were deemed amenable to our needs. Two procedures initially considered were (1) the Weidenhagen route,[10] which calls for treatment of an acyloin with cupric salts in the presence of an aldehyde and aqueous ammonia (eq 2) and (2)



(2)

Bredereck and Theilig's conversion of disubstituted oxazoles to disubstituted imidazoles.[11] Unfortunately, the former method gives rather poor yields of product and the required acyloins were not always readily available. The latter avenue was even more disappointing, perhaps not that surprising in view of the limited selection of substrates examined (i.e., only aryl-substituted oxazoles).

We next focused our attention on a seemingly attractive two-step sequence[12] employing an olefin and commercially available nitrosonium tetrafluoroborate in nitrile media to afford isolable intermediate salts **12** (eq 3). Hydride



(3)

12

R = CH_2Ph, i-C_4H_9

reduction (Red-Al, Aldrich) prior to workup reportedly gives the imidazole in moderate yields. In our hands, numerous attempts at repeating this essentially procedureless communication beyond the point of generating the *N*-hydroxyimidazolium ions **12** were without success. The products realized did show chromatographic and spectral properties (IR, NMR, UV) that are *very* similar to those observed for imidazoles obtained via the Weidenhagen route.[10] Subsequent alkylation likewise proceeded with excellent efficiency (75–98%), and the ratios of 1,2,4- to 1,2,5-trisubstituted products were quite high as well. Obtention of mass spectral data, however, revealed that in reality the materials that had been formed were the *N*-hydroxyimidazoles which were then carried on to O-alkylated derivatives, thereby accounting for the appearance of (M^+ + 16) peaks in the mass spectra for both di- and trisubstituted imidazoles prepared in this way. Hence, we returned to the Weidenhagen technology, with hopes of improving this protocol.

While several acyloins were prepared via an epoxide precursor,[13] these were difficult to isolate and yields were usually modest. This was overcome in several important cases by selective bromination of the corresponding methyl ketones in CH_3OH[14] followed by conversion to the α-acetoxy ketone with KOAc. Employing these derivatives as starting materials coupled with other slight modifications (e.g., mode of addition; see Experimental Section) resulted in good to excellent yields of 2,4(5)-disubstituted imidazoles in comparison to those obtained by using existing technology.[10] A complete listing is given in Table I.

Preparation of 1,2,4-Trisubstituted Imidazoles

Reports in the literature on the N-alkylation of disubstituted imidazoles are surprisingly few in number. Aside from an occasional N-methylation or benzylation, there has been no systematic study to our knowledge on the regiochemistry of N-alkylation of 2,4(5)-disubstituted heterocycles of this type. Earlier work dealing with 2-methyl-4(5)-phenylimidazole[15] and benzimidazoles[16] in-

(7) For a discussion on the photooxidation of imidazoles, see: Wasserman, H. H.; Lipshutz, B. H. In "Singlet Oxygen"; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; p 481.

(8) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 241 and references therein.

(9) Casey, M.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1982**, 714.

(10) Weidenhagen, R.; Herrmann, R. *Ber.* **1953**, *68*, 1935. Stoeck, V.; Schunack, W. *Arch. Pharm. (Weinheim, Ger.)* **1976**, *309*, 421. While the majority of imidazoles could be formed by this known route, simply changing the mode of addition [i.e., dissolving the $Cu(OAc)_2$ in 25% NH_4OH and adding this solution dropwise to a solution of the acyloin (or acetoxy ketone) and aldehyde in 25% NH_4OH at 0 °C; gradual heating from 0 to 100 °C] resulted in substantially improved yields, as listed in Table I.

(11) Bredereck, H.; Theilig, G. *Ber.* **1953**, *86*, 88. Theilig, G. *Ibid.* **1953**, *86*, 96.

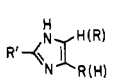
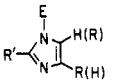
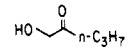
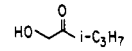
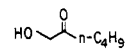
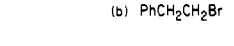
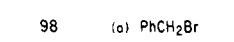
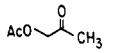
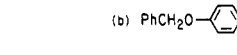
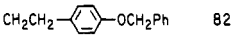
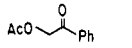
(12) Scheinbaum, M. L.; Dines, M. B. *Tetrahedron Lett.* **1971**, 2205.

(13) Tsuji, T. *Tetrahedron Lett.* **1966**, 2413. Santosusso, T. M.; Swern, D. *Ibid.* **1968**, 4261.

(14) Gaudry, M.; Marquet, A. *Bull. Soc. Chim. Fr.* **1967**, 1850. Marquet, A.; Dvolaitzky, M.; Kagan, H.; Mamkok, L.; Ouannes, C.; Jacques, J. *Ibid.* **1961**, 1822.

(15) Glover, E. E.; Pointer, D. J. *Chem. Ind. (London)* **1976**, 413.

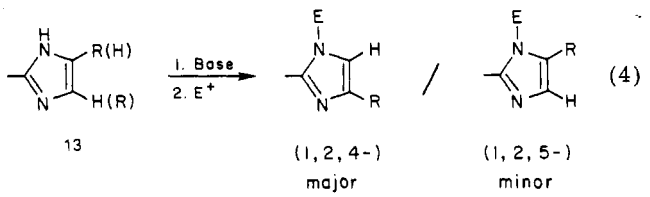
Table I. Preparation and Alkylation of 2,4(5)-Disubstituted Imidazoles

entry	acyloin	imidazole	yield,[a] %	electrophile	product(s)[a]	yield, %	ratio[b]	NMR data	
							1,2,4- : 1,2,5-	C-5H : C-4H	
1		R = n-C_3H_7, R' = CH_3	36	n-BuBr	E = n-Bu	92	92:8[c]	6.41	6.50
2		R = i-C_3H_7, R' = CH_3	88	PhCH=CHCH$_2$Cl	E = CH_2CH=CHPh	90	84:16	6.52	6.70
3		R = n-C_4H_9, R' = CH_3	41	(a)	E = i-C_3H_7	84	100:0		
				(b) PhCH$_2$CH$_2$Br	E = CH_2CH_2Ph	76	100:0		
4		R = i-C_4H_9, R' = CH_3	69	(a) 	E = 	78	100:0		
				(b)	E = CH_2CH=CH_2	78	100:0		
		R = i-C_4H_9, R' = H	84		E = CH_2CH=CH_2	77	100:0		
5		R = t-C_4H_9, R' = CH_3	98	(a) PhCH$_2$Br	E = CH_2Ph	93	100:0		
				(b) 	E = 	72	100:0		
				(c) CH_3I	E = CH_3I	89	87:13[c]	6.55	6.71
				(d) PhCH=CHCH$_2$Cl	E = CH_2CH=CHPh	89	100:0		
		R = t-C_4H_9, R' = H	94	CH_3I	E = CH_3	97	78:22[c]	6.60	6.76
6		R = CH_3, R' = CH_3	82	(a) PhCH$_2$Br	E = CH_2Ph	96	89:11[c]	6.51	6.69
				(b) 	E = 	82	97:3	6.52	6.65
7		R = Ph, R' = CH_3	72	PhCH$_2$Br	E = CH_2Ph	98	100:0		

[a] Isolated, chromatographically pure material. [b] Determined by 300-MHz NMR. [c] This ratio was also obtained by VPC analysis on a 6 ft × 1/8 in. SE-30 column.

dicates that N-methylation should lead to mixtures of 1,2,4- and 1,2,5-trisubstituted isomers (85:15 in the former, 45:55–60:40 with the latter case, depending upon aryl substitution), while N-benzylation of 2,4(5)-dimethylimidazole gives an 88:12 mixture of products.[17] Elaborate schemes have been devised to specifically generate *N*-methyl-2,4-dialkyl-[18] or 1,2,5-trialkylimidazoles.[19] These data relating to the regiochemistry of N-alkylation served solely as foreshadowing to our more extensive general study, the results of which would be crucial in determining the outcome of subsequent reactions with singlet oxygen (Scheme II).

In essence, N-alkylation of 2,4(5)-dialkylimidazoles **13** proceeded in a remarkably straightforward manner, granting excellent yields of trisubstituted materials (eq 4).



(4)

13 (1,2,4-) major / (1,2,5-) minor

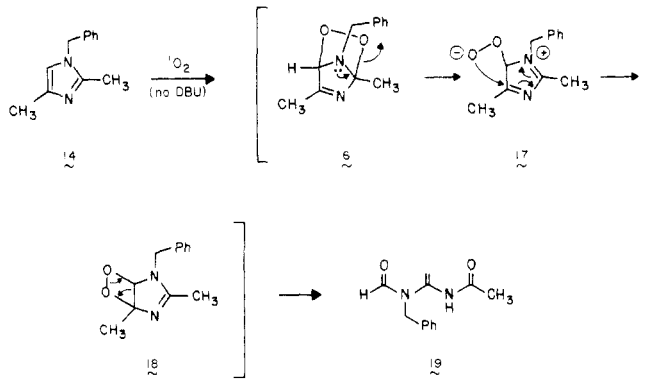
It was necessary for solubility reasons to predissolve the starting disubstituted imidazole in dry DMF at room temperature and then to simply add this solution via cannula to a slurry of NaH (3 equiv) in THF containing 1.1 equiv of an electrophile. The reactions were complete in less than 30 min, and by TLC only a single product in most cases could be detected. Filtration through SiO_2 removed excess alkylating agent and afforded chromatographically pure materials. Several combinations of imidazoles and electrophiles that participate in this coupling are listed in Table I.

Each newly formed trisubstituted product was fully characterized and analyzed by 300-MHz ^{1}H NMR and in many cases by VPC, as to isomer content. The desired isomer was routinely found to be by far the major product of each alkylation, with most imidazoles being formed exclusively as the 1,2,4-trisubstituted material. Earlier work had shown that at 60 MHz a 1,2,4 and 1,2,5 mix is not always fully resolved, and hence chiral shift reagents had to be employed.[15] From this previous analysis it is apparent that the proton at C-5 in the 1,2,4 series appears to resonate at ca. 0.1 ppm upfield relative to that at C-4 in the 1,2,5-trisubstituted isomer. The percent of each isomer present was then simply determined by integration of the signals (two singlets) corresponding to these protons in the NMR spectrum. Furthermore, for those compounds that could be passed through a VPC, the ratios obtained matched perfectly with those seen by ^{1}H NMR analysis (see Table I). In addition, subsequent singlet oxygenation served as a chemical corroboration for our assignment (vide infra).

Insofar as the ratios formed (Table I) are concerned, it is apparent that the steric nature of both the alkyl substituent at C-4 and the electrophile play a pivotal role in determining the regiochemistry of N-alkylation. Comparison of both entries 5a and 6a, where only the C-4 residue differs, and entries 6a and 6b, where size of the electrophile is the factor, supports this hypothesis. Methylation of 2-methyl-4(5)-phenylimidazole is known to

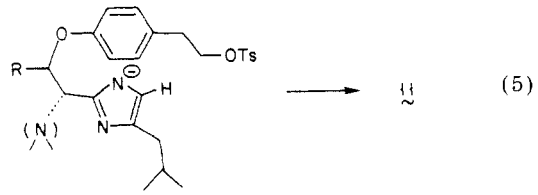
(16) Mathias, L. J.; Burkett, D. *Tetrahedron Lett.* **1979**, 4709.
(17) Godefrei, E. F. *J. Org. Chem.* **1968**, *33*, 860.
(18) Masui, M.; Miyata, H.; Suda, K.; Yamauchi, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1960.
(19) Godefrei, E. F.; Mentjens, J. H. F. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 56.

Scheme IV



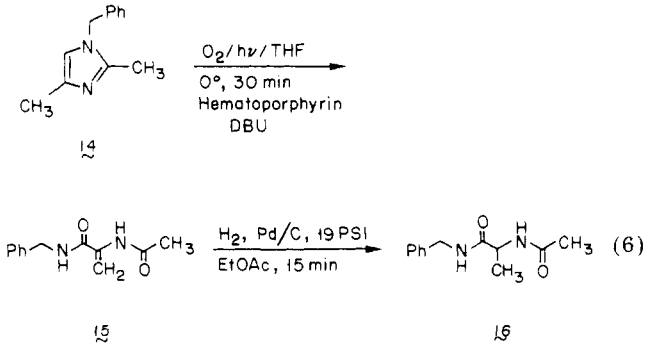
produce an 85:15 mixture,[15] while use of benzyl bromide in place of Me_2SO_4 leads exclusively to the *N*-benzyl-2-methyl-4-phenyl derivative (entry 7). As a check on our means of analysis, we found that benzylation of 2,4(5)-dimethylimidazole (entry 6a) afforded an 89:11 ratio of products, in excellent agreement with the reported value (88:12).[17]

Several of the findings outlined in Table I are particularly noteworthy and deserve comment. While the efficiency of N-alkylation is quite good (72–98%) considering that only ca. 1.1 equiv of an electrophile was used, high yields are not restricted to activated electrophiles. Indeed, both *n*-butyl bromide and isopropyl iodide participate readily. As the alkylation conditions are mild, other functional groups may be tolerated (e.g., entry 5b). The result that we found quite exciting centers around entry 4a. It is most encouraging to see that the imidazolate anion acts entirely in the nucleophilic mode even in an intermolecular reaction without competition from an elimination pathway. This result suggests that macrocycle formation via intramolecular N-alkylation to target structure **11** under conditions of dilution is a viable route to the phencyclopeptine backbone (eq 5).



(5)

Finally, we disclose some of our preliminary work on the utility of 1,2,4-trisubstituted imidazoles in synthesis. Treatment of a THF solution of *N*-benzyl-2,4-dimethylimidazole (**14**), containing 2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 °C with molecular oxygen in the presence of light and hematoporphyrin as sensitizer[7] gave rise to diamide **15** in ca. 95% yield (eq 6). Rather



(6)

than handling this material, it was more convenient to replace the THF with clean EtOAc and hydrogenate the reaction mixture directly in a Parr apparatus. Uptake was rapid and afforded alanine derivative **16** in 83% overall yield, identical in all respects (TLC, IR, NMR, MS) with an authentic sample prepared by conventional procedures. Quite unexpectedly, effecting the same process *without* DBU in the reaction vessel led to a completely different mode of imidazole cleavage. The only detectable product formed in this case, judging from both TLC and NMR analysis of the "crude" reaction mixture is the bis(amide) ketene acetal species **19**. Presumably **19** arises by way of isomerization of the same endoperoxide (i.e., **6**) to dioxetane **18** via **17**, which leads to **19** (Scheme IV). Clearly, the presence of base is sufficient to prevent this undesired rearrangement, perhaps by slowing down the initial uptake of $^1O_2$, as amines are well-known quenching agents of singlet oxygen.[20] Control experiments performed under identical conditions but without sensitizer or light led to no consumption of starting material in either case. The scope of this new methodology, including dipeptide generation (i.e., where C-2 in **13** bears an aminomethyl group) and induction of chirality during hydrogenation of the dehydrodiamide/dipeptide, as well as applications in natural products synthesis, will be reported in due course.

Experimental Section

NMR spectra were recorded on a Varian T-60, FT-80, or a Nicolet NT-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard unless specified otherwise. Infrared spectra were obtained with a Perkin-Elmer 283 grating spectrophotometer. Mass spectra were measured at 70 eV on a Zab 2F spectrometer. Melting points were determined on a Fischer Johns hot-stage apparatus and are uncorrected. All solvents, olefins, and volatile alkylating agents were freshly distilled prior to use. Nitrosonium tetrafluoroborate ($NOBF_4$), Red-Al (70% in toluene), DBU, and acetaldehyde were obtained from Aldrich and were used as received. Sodium hydride (50% in oil) was purchased from Alfa; cupric acetate was obtained from Mallinckrodt. All reactions were carried out under a blanket of argon. Column chromatography was performed with silica gel 60 (Merck, 70–230 mesh). Baker precoated silica gel glass plates (0.25 mm) were used for the monitoring of reactions. Iodine or phosphomolybdic acid/heat was used to visualize chromatograms.

Typical Procedure for the Preparation of 2,4(5)-Disubstituted Imidazoles. (A) The Weidenhagen Procedure.[10] **2,4(5)-Dimethylimidazole.** Acetol acetate (5.8 g, 0.05 mol) was added to a vigorously stirred solution of 20 g (0.100 mol) of copper(II) acetate in 100 mL of 25% NH_4OH containing 3.0 g (0.068 mol) of acetaldehyde. A greyish blue precipitate (5.0 g, 0.031 mol) is formed upon heating to 100 °C for 15–20 min, this being the intermediate copper(I) salt of the 2,4(5)-dimethylimidazole. A hot aqueous suspension (100 mL of H_2O) of this salt is treated with gaseous H_2S for 10–15 min, filtered, and allowed to cool. The solution is then extracted with CH_2Cl_2 (2×) and dried ($MgSO_4$). Concentration in vacuo and distillation (0.02 mmHg, 120 °C) gives 2.95 g (0.03 mol) of the free base: mp 92–93 °C (lit.[9] mp 92 °C); R_f (1:1 EtOH/$CHCl_3$) 0.36; IR (neat) cm^{-1} 1620, 1080, 750; NMR δ 6.25 (s, 1 H), 2.41 (s, 3 H), 2.27 (s, 3 H); mass spectrum, *m/e* (relative abundance) 96 (100, M^+), 95 (61), 55 (22), 54 (49), 42 (42).

2-Methyl-4(5)-*n*-propylimidazole: mp 61–62 °C; R_f (1:1 EtOH/$CHCl_3$) 0.50; IR (neat) cm^{-1} 2950, 1620, 1400, 1140, 750; NMR (partial) δ 6.73 (s, 1 H), 2.50 (s, 3 H), 1.01 (d,3 H, J = 11 Hz); mass spectrum, *m/e* (relative intensity) 124 (M^+, 24), 109 (100), 96 (8), 95 (5); calcd for $C_7H_{12}N_2$ 124.1000, found 124.0997.

2-Methyl-4(5)-*n*-butylimidazole: mp 55–57 °C; R_f (1:1 EtOH/$CHCl_3$) 0.46; IR (neat) cm^{-1} 2940, 2860, 1580, 1420, 1260, 1020, 730; NMR δ 6.60 (s, 1 H), 2.50 (m, 2 H), 2.37 (s, 3 H), 0.96 (d, 3 H, J = 6 Hz); ^{13}C NMR (partial) δ 116, 31.3, 25.9, 22.5, 22.1,

(20) Foote, C. S. In "Singlet Oxygen"; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; Chapter 5, pp 139–171.

(21) Methanolic KOH was used in some examples depending upon solubility of the α-acetoxy ketone.

13.6; mass spectrum, m/e (relative abundance) 138 (M^+, 20), 109 (15), 96 (83), 95 (100); calcd for $C_8H_{14}N_2$ 138.1157, found 138.1157.

4-Isobutylimidazole: mp 71–72 °C (lit.[22] mp 72–73 °C); R_f (1:1 EtOH/$CHCl_3$) 0.63; IR (neat) cm^{-1} 2980, 2880, 1580, 1470, 1260, 1100, 930, 820, 730; NMR (partial) δ 6.61 (s, 1 H), 2.50 (d, 2 H, J = 7 Hz), 0.95 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (partial) 136.3, 118.2, 35.5, 28.5, 22.1; mass spectrum, m/e (relative abundance) 124 (M^+, 20), 82 (62), 81 (100).

2-Methyl-4(5)-*tert*-butylimidazole: mp 138–141 °C; R_f (1:1 EtOH/$CHCl_3$) 0.43; IR (neat) cm^{-1} 2980, 1620, 1560, 1200, 1020, 740, 640; NMR δ 6.61 (s, 1 H), 2.30 (s, 3 H), 1.31 (s, 9 H); ^{13}C NMR (partial) 137.1, 118.4, 30.4, 12.9; mass spectrum, m/e (relative abundance) 138 (M^+, 18), 123 (100), 82 (20); calcd for $C_8H_{14}N_2$ 138.1157, found 138.1156. Anal. Calcd for $C_8H_{14}N_2$: C, 69.50; H, 10.21; N, 20.28. Found: C, 69.53; H, 10.62; N, 20.18.

4-*tert*-Butylimidazole:[23] mp 75–78 °C; R_f (1:1 EtOH/$CHCl_3$) 0.39; IR (neat) cm^{-1} 2980, 1620, 1580, 1460, 1360, 1300, 1160, 1105, 1090, 810, 730; NMR δ 7.58 (s, 1 H), 6.79 (s, 1 H), 1.32 (s, 9 H); ^{13}C NMR 145.1, 134.5, 115.4, 30.2; mass spectrum, m/e (relative abundance) 124 (M^+, 18), 109 (100), 82 (8), 81 (8).

2-Methyl-4(5)-phenylimidazole: mp 129–131 °C (lit.[10] mp 129–130 °C); R_f (1:1 EtOH/$CHCl_3$) 0.62; IR (neat) cm^{-1} 3060, 1600, 1420, 1180, 750, 690; NMR δ 7.55 (m, 5 H), 7.24 (s, 1 H), 2.53 (s, 3 H); mass spectrum, m/e (relative intensity) 158 (M^+, 100), 130 (29), 118 (18), 117 (48), 140 (31), 90 (71).

(B) Modified Weidenhagen Procedure. 2-Methyl-4(5)-isopropylimidazole. 1-Acetoxy-3-methyl-2-butanone (0.375 mL, 2.60 mmol) was dissolved in 5 mL of 3 N aqueous KOH[21] at 0 °C. A mixture of 5.1 g of cupric acetate, 70 mL of 25% NH_4OH, and 4.1 mL (13.2 mmol) of acetaldehyde, all at 0 °C, was added to the acyloin solution. The resulting mixture was shaken vigorously and heated intermittently to 100 °C until a blue-green precipitate appeared. The suspension was allowed to cool to 25 °C over several hours and then cooled to 0 °C to allow further precipitation. After 6 h at 0 °C, the mixture was filtered, washed once with EtOH, and air-dried to afford 454 mg (2.39 mmol) of the intermediate blue-white copper(I) salt of 2-methyl-4(5)-isopropylimidazole.

A hot aqueous suspension (100 mL) of this salt was treated with gaseous H_2S for 15–20 min, filtered, rinsed with hot H_2O, and allowed to cool. Concentration in vacuo yielded 307 mg (2.28 mmol) of the free base (88%): mp 91–94;[24] R_f (1:1 EtOH/$CHCl_3$) 0.40; IR (neat) cm^{-1} 2980, 1580, 1420, 1110, 1020, 730; NMR δ 6.59 (s, 1 H), 2.88 (m, 1 H), 2.37 (s, 3 H), 1.28 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR 143.6, 142.7, 114.6, 26.3, 22.3, 13.4; mass spectrum, m/e (relative abundance) 124 (31, M^+), 110 (6), 109 (100), 96 (4), 95 (5), 68 (20); calcd for $C_7H_{12}N_2$ 124.1000, found 124.1002.

2-Methyl-4(5)-isobutylimidazole: R_f (1:1 EtOH/$CHCl_3$) 0.50; IR (neat) cm^{-1} 2960, 1600, 1510, 1470, 1020, 800, 740; NMR δ 6.57 (s, 1 H), 2.41 (d, 2 H, J = 5 Hz), 2.31 (s, 3 H), 1.75 (m, 1 H), 0.89 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR 145.0, 136.3, 119.1, 37.2, 30.0, 23.8, 14.9; mass spectrum, m/e (relative abundance) 138 (M^+, 19), 123 (4), 96 (50), 95 (100); calcd for $C_8H_{14}N_2$ 138.1157, found 138.1154.

Representative Procedure for the N-Alkylation of 2,4-(5)-Disubstituted Imidazoles. 1-Benzyl-2-methyl-4-*tert*-butylimidazole. To sodium hydride (137 mg, 50% in oil, 2.86 mmol), washed three times with pentane under Ar, was added dry THF (3 mL) followed by benzyl bromide (2.10 mmol). A solution of 2-methyl-4(5)-*tert*-butylimidazole (1.91 mmol), predissolved in dry DMF (1.9 mL), was added slowly via cannula to the suspension. The reaction was allowed to stir for 2 h and then was cautiously quenched with EtOH at 0 °C. Extraction with Et_2O (2×), drying the combined extracts ($MgSO_4$), and concentration in vacuo was followed by chromatography on silica gel with Et_2O to afford 409 mg (1.77 mmol, 93%) of white solid: mp 59–62 °C; R_f (Et_2O) 0.23; IR (neat) cm^{-1} 2960, 2880, 1500, 1455, 1420, 1360, 1200, 1030, 930, 730, 700; NMR δ 7.15 (m, 5 H), 6.46 (s, 1 H), 4.91 (s, 2 H), 2.29 (s, 3 H), 1.23 (s, 9 H); ^{13}C NMR 149.5, 143.7, 136.0, 128.5, 127.5, 126.3, 113.0, 49.2, 29.7, 12.1; mass spectrum, m/e (relative abundance) 228 (M^+, 18), 214 (11), 92 (8), 91 (100); calcd for $C_{15}H_{20}N_2$ 228.1625, found 228.1621.

1-*n*-Butyl-2-methyl-4-*n*-propylimidazole: R_f (Et_2O) 0.25; IR (neat) cm^{-1} 2960, 1760, 1420, 730; NMR (partial) δ [6.50 (s, minor isomer), 6.41 (s, major isomer), 1 H], 2.31 (s, 3 H); mass spectrum, m/e (relative abundance) 179 (15), 165 (20), 152 (100), 151 (25), 110 (15), 109 (15), 95 (40); calcd for $C_{11}H_{19}N_2$ (M^+ – H) 179.1548, found 179.1539.

1-Cinnamyl-2-methyl-4-isopropylimidazole: R_f (1:1 Et_2O/EtOAc) 0.09; IR (neat) cm^{-1} 2960, 1420, 960; NMR (partial) δ 7.31 (m, 5 H), [6.70 (s, minor isomer), 6.52 (major isomer), 1 H], 6.20 (m, 2 H), 4.53 (d, 2 H, J = 4 Hz), 2.37 (s, 3 H), 1.27 (s, 3 H), 1.19 (s, 3 H); mass spectrum, m/e (relative abundance) 240 (M^+, 20), 117 (100), 115 (25), 91 (21); calcd for $C_{16}H_{20}N_2$ 240.1626, found 240.1622.

1-Isopropyl-2-methyl-4-*n*-butylimidazole: R_f (1:1 Et_2O/EtOAc) 0.15; IR (neat) cm^{-1} 2940, 1460; NMR (partial) δ 6.61 (s, 1 H), 2.44 (s, 3 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 0.92 (t, 3 H, J = 4 Hz); mass spectrum, m/e (relative abundance) 180 (M^+, 22), 179 (25), 138 (80), 128 (40), 95 (100); calcd for $C_{11}H_{20}N_2$ 180.1626, found 180.1626.

1-(2-Phenethyl)-2-methyl-4-*n*-butylimidazole: R_f (EtOAc) 0.85; IR (neat) cm^{-1} 2980, 2960, 2870, 1600, 1512, 1500, 1455, 1420, 1360, 1078, 1030, 995, 750, 700; NMR δ 7.13 (m, 5 H), 6.45 (s, 1 H), 3.98 (t, 2 H, J = 5 Hz), 2.96 (t, 2 H, J = 5 Hz), 2.10 (s, 3 H), 0.93 (t, 3 H, J = 4 Hz); ^{13}C NMR (partial) 130.0, 129.9, 128.3, 115.9, 48.8, 38.9, 33.1, 29.4, 23.8, 15.3, 14.0; mass spectrum, m/e (relative abundance) 228 (M^+, 5), 213 (13), 200 (100), 105 (58); calcd for $C_{15}H_{20}N_2$ 242.1782, found 242.1783.

1-[(*p*-Benzyloxy)phenethyl]-2-methyl-4-isobutylimidazole: R_f (1:1 Et_2O/EtOAc) 0.08; IR (neat) cm^{-1} 2960, 2880, 1510, 1418, 1240, 1175, 1010, 820, 730; NMR δ 7.35 (s, 5 H), 6.86 (s, 4 H), 6.42 (s, 1 H), 5.00 (s, 2 H), 3.91 (t, 2 H, J = 6 Hz), 2.86 (t, 2 H, J = 6 Hz), 2.05 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (partial) 137.0, 130.1, 129.9, 129.7, 128.5, 127.8, 127.3, 115.2, 70.1, 47.5, 37.5, 36.5, 28.4, 22.4; mass spectrum, m/e (relative abundance) 348 (M^+, 15), 333 (3), 306 (27), 305 (17), 211 (6), 200 (5), 151 (6), 149 (6), 108 (10), 91 (100); calcd for $C_{23}H_{28}N_2O$ 348.2202, found 348.2200.

1-Allyl-2-methyl-4-isobutylimidazole: R_f (1:1 Et_2O/EtOAc) 0.10; IR (neat) cm^{-1} 2980, 2880, 1510, 1415, 1171, 990, 730; NMR (partial) δ 6.41 (s, 1 H), 5.72 (m, 1 H), 4.27 (d, 2 H, J = 5 Hz), 2.25 (s, 3 H), 0.88 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (partial) 132.8, 117.0, 116.2, 48.0, 37.4, 28.2, 22.2, 12.5; mass spectrum, m/e (relative abundance) 178 (M^+, 23), 175 (37), 136 (52), 135 (100), 95 (22), 94 (17); calcd for $C_{11}H_{18}N_2$ 178.1470, found 178.1464.

1-Allyl-4-isobutylimidazole: R_f (1:1 Et_2O/EtOAc) 0.10; IR (neat) cm^{-1} 2960, 2870, 1500, 1370, 1160, 1110, 980, 920, 810; NMR (partial) δ 7.45 (s, 1 H), 6.70 (s, 1 H), 6.00 (m, 1 H), 5.39 (m, 1 H) 4.51 (dd, 2 H, J = 1, 4 Hz), 1.08 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (partial) 133.1, 118.1, 117.5, 49.2, 37.7, 28.5, 22.4; mass spectrum, m/e (relative abundance) 164 (M^+, 25), 122 (80), 121 (90), 95 (27); calcd for $C_{10}H_{16}N_2$ 164.1313, found 164.1324.

1-[(*p*-Benzyloxy)phenethyl]-2-methyl-4-*tert*-butylimidazole: mp 71–73 °C ; R_f (Et_2O) 0.12; IR (neat) cm^{-1} 2960, 2860, 1610, 1510, 1452, 1415, 1378, 1355, 1300, 1238, 1172, 1010, 740, 700; NMR δ 7.42 (s,5 H), 6.95 (s, 4 H), 6.45 (s, 1 H), 5.08 (s, 2 H), 3.93 (t, 2 H, J = 5 Hz), 2.89 (t, 2 H, J = 5 Hz), 2.18 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR 150.2, 143.1, 136.8, 129.9, 129.4, 128.2, 127.6, 127.0, 114.9, 112.0, 69.8, 47.3, 36.3, 30.0, 12.5; mass spectrum, m/e (relative abundance) 348 (M^+, 30), 333 (60), 136 (10), 91 (100); calcd for $C_{23}H_{28}N_2O$ 348.2202 found 348.2201. Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.26; H, 8.10; N, 8.04; found: C, 79.07; H, 8.34; N, 8.00.

1,2-Dimethyl-4-*tert*-butylimidazole: R_f (1:1 EtOH/$CHCl_3$) 0.24; IR (neat) cm^{-1} 2980, 2880, 1530, 1470, 1370, 1252, 1110, 910, 730; NMR δ [6.71 (s, minor isomer), 6.55 (s, major isomer), 1 H], 3.72 (s, 3 H), 2.59 (s, 3 H), 1.24 (s, 9 H); mass spectrum, m/e (relative abundance) 152 (M^+, 17), 138 (11), 137 (100), 73 (33); calcd for $C_9H_{16}N_2$ 152.1235, found 152.1231.

1-Cinnamyl-2-methyl-4-*tert*-butylimidazole: mp 125–127 °C; R_f (1:1 Et_2O/EtOAc) 0.25; IR (neat) cm^{-1} 2980, 2870, 1420, 1360, 1265, 1195, 970, 730; NMR δ 7.38 (s, 5 H), 6.60 (s, 1 H), 6.42 (s, 1 H), 6.35 (s, 1 H), 4.55 (d, 2 H, J = 5 Hz), 2.43 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (partial) δ 143.4, 132.5, 132.3, 128.5, 127.9, 126.4, 124.0, 112.5, 47.8, 30.0, 12.8; mass spectrum, m/e (relative abundance) 254 (M^+, 15), 239 (18), 117 (100), 91 (22); calcd for $C_{17}H_{22}N_2$ 254.1782, found 254.1783. Anal. Calcd for $C_{17}H_{22}N_2$:

(22) Akabari, S.; Numano, S. *J. Chem. Soc. Jpn.* **1932**, *53*, 200.
(23) Jackman, M.; Klenk, M.; Fishburn, B.; Tullar, B. F.; Archer, S. *J. Am. Chem. Soc.* **1948**, *70*, 2884.
(24) Isolated previously as its picrate, mp 175–176 °C: Matsuura, T.; Banaba, A.; Ogura, K. *Tetrahedron* **1971**, *27*, 1211.

C, 80.26; H, 8.72; N, 11.02. Found: C, 80.03; H, 8.83; N, 11.08.

1-Methyl-4-*tert*-butylimidazole: R_f (1:1 EtOH/$CHCl_3$) 0.40; IR (neat) cm^{-1} 2980, 2180, 1560, 920, 730; NMR (partial) δ [7.39 (s, minor isomer), 7.35 (major isomer), 1 H], [6.76 (s, minor isomer), 6.60 (s, major isomer), 1 H], [4.03 (s, minor isomer), 3.98 (s, major isomer), 3 H], 1.44 (s, 9 H); mass spectrum, *m/e* (relative abundance) 138 (M^+, 10), 137 (22), 123 (30), 88 (65), 84 (100); calcd for $C_8H_{14}N_2$ 138.1157, found 138.1145.

1-Benzyl-2,4-dimethylimidazole:[17] R_f (Et_2O) 0.14; IR (neat) cm^{-1} 2910, 1670, 1510, 1410, 1200, 1140, 730, 710; NMR (partial) δ [6.69 (s, minor isomer), 6.51 (s, major isomer), 1 H], 4.95 (s, 2 H), 2.28 (s, 3 H), 2.16 (d, 3 H, J = 0.5 Hz); mass spectrum, *m/e* (relative abundance) 186 (M^+, 89), 92 (10), 91 (100), 65 (12).

1-[(*p*-Benzyloxy)phenethyl]-2,4-dimethylimidazole: R_f (Et_2O) 0.03; IR (neat) cm^{-1} 2920, 1610, 1510, 1240, 750; NMR δ [6.65 (s, minor isomer), 6.52 (s, major isomer), 1 H], 5.02 (s, 2 H), 3.57 (t, 2 H, J = 6 Hz), 2.90 (t, 2 H, J = 6 Hz), 2.18 (s, 3 H), 2.07 (s, 3 H); mass spectrum, *m/e* (relative abundance) 306 (M^+, 10), 131 (20), 107 (12), 91 (26); calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1726.

1-Benzyl-2-methyl-4-phenylimidazole: R_f (Et_2O) 0.32; IR (neat) cm^{-1} 3060, 1600, 1420, 1180, 750, 690; NMR (partial) δ 7.11 (s, 1 H), 5.05 (s, 2 H), 2.38 (s, 3 H); mass spectrum, *m/e* (relative abundance) 248 (M^+, 85), 157 (5), 92 (14), 91 (100), 89 (10); calcd for $C_{17}H_{16}N_2$ 248.1314, found 248.1309.

Photooxidation of 1-Benzyl-2,4-dimethylimidazole. Preparation of *N*-acetylalanine-*N*-benzylamide. A solution of the imidazole (26.5 mg, 0.142 mmol) in 4 mL of dry THF containing 30 μL (0.20 mmol) of DBU and ca. 2 mg of hematoporphyrin is fitted with a gas dispersion tube through which dry oxygen is continuously passed.[25] The solution is cooled in an ice bath and irradiated externally with a 275-W sunlamp for 30 min while maintaining the reaction temperature (ca. 1–5 °C). Following consumption of the starting material as monitored by TLC, the mixture was concentrated in vacuo, diluted with 15 mL of distilled EtOAc, and transferred to a hydrogenation vessel (Parr apparatus) containing palladium on charcoal as catalyst. Hydrogenation at 19 psi for 15 min followed by rotary evaporation of the solvent and filtration through silica gel (5% EtOAc/Et_2O) afforded 22.7 mg of the desired diamide (83% yield based on 87% purity of the starting imidazole), identical by TLC, IR, NMR, and MS with an authentic sample prepared from alanine via standard amino acid chemistry.

The intermediate dehydrodiamide could also be isolated and displayed the following properties: R_f (1:1 Et_2O/EtOAc) 0.50; IR (neat) cm^{-1} 3450, 1750, 1650, 1630, 1500, 1380, 1270, 1030, 740, 700; NMR δ 7.32 (s, 5 H), 6.41 (d, 1 H, J = 1 Hz), 5.25 (m, 1 H), 4.47 (d, 2 H, J = 5 Hz), 2.09 (s, 3 H); mass spectrum, *m/e* (relative abundance) 218 (M^+, 9), 200 (3), 175 (7), 131 (6), 130 (6), 106 (100), 91 (55), 79 (6).

N-Acetyl-N'-formyl-N'-benzyl-1,1-ethylenediamine (19): R_f (1:1 Et_2O/EtOAc) 0.53; IR (neat) cm^{-1} 2990, 1750, 1690, 1500, 1380, 1280, 1230, 1020; NMR δ 9.01 (s, 1 H), 7.21 (s, 5 H), 4.82 (s, 2 H), 4.35 (m, 2 H), 2.05 (s, 3 H); mass spectrum, *m/e* (relative abundance) 218 (M^+, 12), 200 (3), 176 (8), 175 (10), 149 (5), 131(7), 130 (6), 106 (100), 91 (64); calcd for $C_{12}H_{14}N_2O_2$ 218.1055, found 218.1057.

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Registry No. **5** (R = H; R_1 = Me; R_2 = Pr), 86921-32-6; **5** (R = H; R_1 = Me; R_2 = *i*-Pr), 37455-52-0; **5** (R = H; R_1 = Me; R_2 = Bu), 29680-52-2; **5** (R = H; R_1 = Me; R_2 = *i*-Bu), 86921-33-7; **5** (R = R_1 = H; R_2 = *i*-Bu), 61893-08-1; **5** (R = H; R_1 = Me; R_2 = *t*-Bu), 42252-94-8; **5** (R = R_1 = H; R_2 = *t*-Bu), 21149-98-4; **5** (R = H; R_1, R_2 = Me), 930-62-1; **5** (R = H; R_1 = Me; R_2 = Ph), 13739-48-5; **5** (R = Bu; R_1 = Me; R_2 = Pr), 86921-34-8; **5** (R = $PhCH{=}CHCH_2$; R_1 = Me; R_2 = *i*-Pr), 86921-35-9; **5** (R = *i*-Pr; R_1 = Me; R_2 = Bu), 86921-36-0; **5** (R = $PhCH_2CH_2$; R_1 = Me; R_2 = Bu), 86921-37-1; **5** (R = *p*-$ClCH_2OC_6H_4CH_2CH_2$; R_1 = Me; R_2 = *i*-Bu), 86921-38-2; **5** (R = $CH_2CH{=}CH_2$; R_1 = Me; R_2 = *i*-Bu), 86921-39-3; **5** (R = $CH_2CH{=}CH_2$; R_1 = H; R_2 = *i*-Bu), 86921-40-6; **5** (R = $PhCH_2$; R_1 = Me; R_2 = *t*-Bu), 86921-41-7; **5** (R = *p*-$PhCH_2OC_6H_4CH_2CH_2$; R_1 = Me; R_2 = *t*-Bu), 86921-42-8; **5** (R = R_1 = Me; R_2 = *t*-Bu), 86921-43-9; **5** (R = $PhCH{=}CHCH_2$; R_1 = Me; R_2 = *t*-Bu), 86921-44-0; **5** (R = Me; R_1 = H; R_2 = *t*-Bu), 86921-45-1; **5** (R = $PhCH_2$; R_1 = R_2 = Me), 52726-31-5; **5** (R = *p*-$PhCH_2OC_6H_4CH_2CH_2$, R_1 = R_2 = Me), 86921-46-2; **5** (R = $PhCH_2$; R_1 = Me; R_2 = Ph), 86921-47-3; **15**, 86921-49-5; **16**, 86921-48-4; **19**, 86921-50-8; BuBr, 109-65-9; $PhCH{=}CHCH_2Cl$, 2687-12-9; $(CH_3)_2CHI$, 75-30-9; $PhCH_2CH_2Br$, 103-63-9; *p*-$PhCH_2OC_6H_4CH_2CH_2OTs$, 86587-62-4; $CH_2{=}CHCH_2Br$, 106-95-6; $PhCH_2Br$, 100-39-0; CH_3I, 74-88-4; $HOCH_2COCH_2CH_2CH_3$, 64502-89-2; $HOCH_2COCH(CH_3)_2$, 36960-22-2; $HOCH_2CO(CH_2)_3CH_3$, 73397-68-9; $HOCH_2COCH_2CH(CH_3)_2$, 68113-55-3; $AcOCH_2COC(CH_3)_3$, 38559-25-0; $AcOCH_2COCH_3$, 592-20-1; $AcOCH_2COPh$, 7250-94-4; CH_3CHO, 75-07-0; CHO, 50-00-0.

(25) For a description of the apparatus used, see: Foote, C. S.; Vickers, R. S. *Boll. Chim. Farm.* **1970**, *109*, 599.

Ene-Ene-Retroene Conversion of (-)-β-Pinene to (+)-β-Selinene

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(-)-β-Pinene undergoes an ene reaction with acryloyl chloride at 70 °C to afford 6,6-dimethylbicyclo[3.1.1]-hept-2-ene-2-butanoyl chloride (**2**) in better than 80% yield. Cyclization of **2** to 10,10-dimethyltricyclo-[7.1.1.$0^{2,7}$]undec-2(7)-en-6-one (**4**) by way of an intramolecular ene reaction involving a ketene intermediate occurs on heating with tributylamine at 150 °C. Unsaturated ketone **4** undergoes a clean retroene reaction to yield (+)-7-(2-propenyl)-Δ^9-decal-1-one (**11**) on brief heating at 265 °C. Lithium dimethylcuprate addition to **11** yields a mixture of four isomeric 7-(2-propenyl)-10-methyl-1-decalones (**15**–**18**) where the isomers having the desired cis relationship between the angular methyl and the 2-propenyl groups comprise ca. 75% of the product. Treatment of the ketone mixture with methylenetriphenylphosphorane completes the synthesis of (+)-β-selinene.

We have observed that acryloyl chloride undergoes an ene reaction[1,2] with β-pinene (**1**) under relatively mild conditions to yield adduct (**2**) in high yield (Scheme I). Herein we report the use of **2** in a stereoselective synthesis

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