Chiral Azole Derivatives. 2.[1] Synthesis of Enantiomerically Pure 1-Alkylimidazoles†

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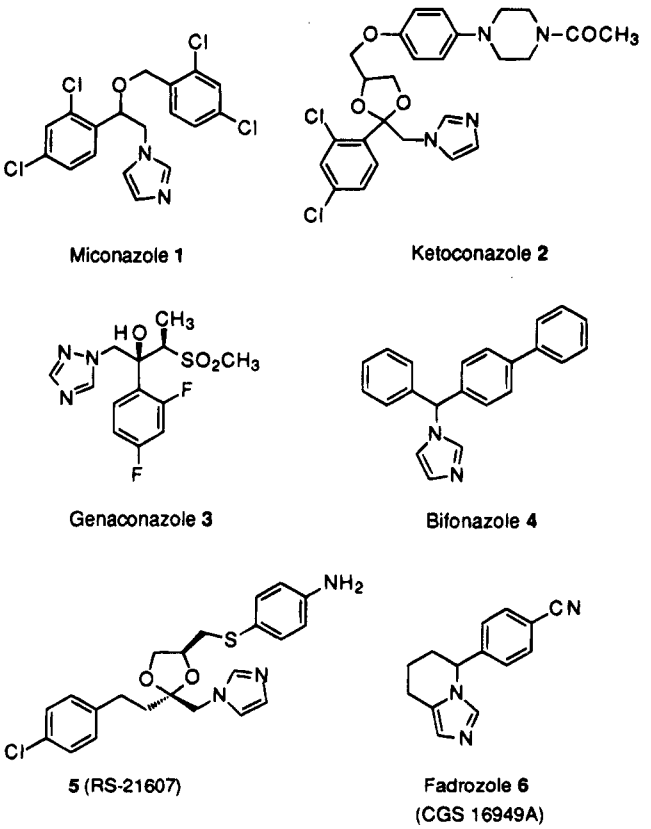
4,5-Dicyanoimidazole has been reacted with racemic and enantiopure alcohols **7** (entries 1–7 in Table 1) under Mitsunobu conditions to give 1-alkyl-4,5-dicyanoimidazole derivatives **8**, which in turn have been transformed by hydrolysis and decarboxylation into 1-alkylimidazoles **10** in good overall yield and high enantiomeric excess. In contrast, when applied to benzyl and benzhydryl alcohols (entries 8–15), this sequence afforded the final compounds in good overall yield, but as racemic mixtures. The 1-(1-phenylalkyl)imidazole derivative (*S*)-(+)-**24** was, however, prepared in enantiopure form starting from the corresponding (*S*)-(−)-α-methylbenzylamine (**21**) using the Marckwald procedure, which entailed the alkylation of **21** with bromoacetaldehyde dimethyl acetal, followed by the construction of the imidazole ring through reaction with potassium thiocyanate and final Ra-Ni desulfuration. Following the same procedure, (*S*)-(+)-**10c** was also synthesized, proving the stereochemical outcome of the Mitsunobu reaction.

Introduction

1-Substituted azoles (imidazoles and 1,2,4-triazoles) such as miconazole (**1**), ketoconazole (**2**), genaconazole (**3**), and bifonazole (**4**) (Chart 1) have become well-established drugs for the treatment of many mycotic infections,[2] whose incidence has been increasing recently due to an increase in the number of immunocompromised hosts.[3]

The antifungal activity of azoles stems from blockade of the conversion of lanosterol to ergosterol, which is necessary for maintaining the integrity of the organism's cell membrane. The specific point of chemical intervention appears to involve inhibition of the cytochrome P-450 enzyme responsible for the oxidative removal of the C-14 methyl group of lanosterol (lanosterol 14α-demethylase).[4] Ketoconazole (**2**) has shown a similar inhibitory effect on the corresponding enzyme responsible for conversion of lanosterol to cholesterol in mammals[5] and has been demonstrated to lower cholesterol in humans.[6] Very recently, the preparation and biological activity of the first nonsteroidal selective inhibitor of mammalian lanosterol 14α-demethylase, compound **5** (RS-21607), have been reported as a potential strategy for cholesterol lowering in man.[7] In addition, **2** has been shown to inhibit a number of other cytochrome P-450 dependent enzymes involved in steroidogenesis and drug metabolism.[8–10] Finally, inhibition of the cytochrome P-450 enzyme aromatase has been identified as a good therapeutic strategy for the treatment of estrogen-dependent breast cancers.[11] These efforts have resulted

Chart 1



* To whom correspondence should be addressed.

† Dedicated to Professor Marino Artico on the occasion of his 60th birthday.

‡ Menarini Ricerche Sud SpA.

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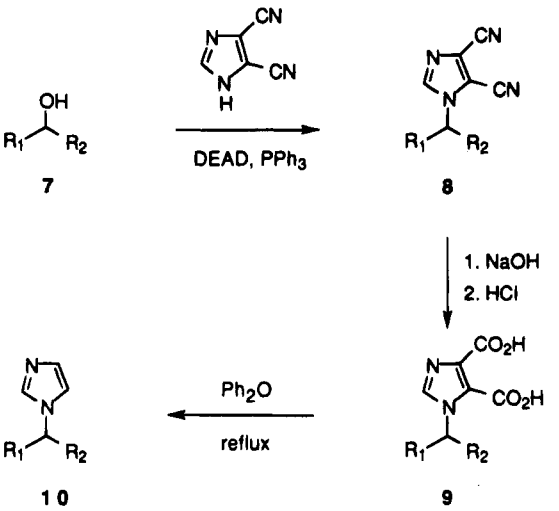
in the identification of structurally diverse aromatase inhibitors, among which some azole compounds (exemplified by fadrozole[12] (**6**) (CGS 16949A)), proved to be potent, long-acting, and selective inhibitors.

Most of the azole derivatives able to inhibit cytochrome P-450 enzymes possess at least one stereogenic center. There are numerous known examples of different pharmacological properties between stereoisomers[13] and, in the wake of the new FDA guidelines, many efforts are currently directed toward the development of enantiomerically pure drugs.[14] However, there is limited information in the literature on the preparation of enantiomers of azole compounds, either by stereoselective synthesis[15] or enantiomeric separation.[16] In particular, to our knowledge, only a few examples of enantiopure azole derivatives having the azole moiety directly linked to the stereogenic center have as yet been reported, most likely because of difficulties in their preparation.

During the course of our studies on antifungal agents[17] we became interested in developing methodologies for the preparation of these compounds in chiral form for subsequent biological evaluation following the new FDA guidelines.

N-Alkylimidazoles are usually prepared by alkylating imidazole derivatives or the corresponding imidazolate ions with electrophiles, but this method suffers from two major problems: it generally affords a mixture of regioisomers, complicating further transformation unless a separation step is included, and cannot be applied to electrophiles which readily undergo elimination reactions. Moreover, when the stereogenic center is involved in the substitution by imidazole, the control of the stereochemical course of the alkylation is troublesome and, to the best of our knowledge, no general procedure had been published before our communication.[1] We wish to report in detail in this publication the preparation of enantiomerically pure imidazole derivatives *via* Mitsunobu reactions as well as an alternative methodology based on the Marckwald procedure which, for the first time, has been applied to chiral amines.

Scheme 1



For R_1, R_2 and stereochemistry see Tables 1 and 2.

Results and Discussion

Mitsunobu–Hydrolysis–Decarboxylation Sequence. We envisaged in the Mitsunobu reaction[18] a possibility of synthesizing azoles bearing an imidazole moiety directly linked to a stereogenic center. Although it has been applied to a wide range of nucleophiles, including some heterocyclic compounds,[19–21] to our knowledge the Mitsunobu reaction has not been used for the *N*-alkylation of imidazole derivatives. The only information (no experimental details) in this regard concerns the reaction of both imidazole and 2-methyl-4(5)-nitroimidazole with methanol and 2-phenylethanol: while imidazole itself is unreactive under the usual reaction conditions, the nitroimidazole derivative reacts to give a mixture of *N*-alkyl-2-methyl-4-nitroimidazole and the corresponding 5-nitro isomer.[18] Consequently, we decided to investigate the possibility of performing the alkylation of a suitable imidazole derivative with alcohols **7** *via* the Mitsunobu reaction (Scheme 1). For this purpose we chose the commercially available 4,5-dicyanoimidazole (DCI) as the imidazole substrate, since because it is symmetrically substituted with two "activating", electron-withdrawing groups it cannot give rise to a mixture of regioisomers and because of the possibility of converting the Mitsunobu reaction products **8** into the desired *N*-alkylimidazoles **10** by hydrolysis and decarboxylation. In order to establish the stereochemical outcome of the Mitsunobu reaction we used both racemic and enantiopure alcohols as the alkylating agents.

Alcohols **7g–i**, which are not commercially available, were prepared from the corresponding ketones by reduction with $NaBH_4$ ((±)-**7g–i**) or by asymmetric reduction ((+)-**7h,i**) with $LiAlH_4$ partially decomposed with a chiral amino alcohol, following the procedure recently described

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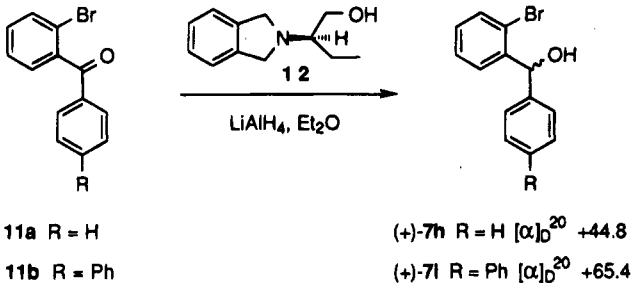
Scheme 2



11a R = H (+)-**7h** R = H $[\alpha]_D^{20}$ +44.8

11b R = Ph (+)-**7i** R = Ph $[\alpha]_D^{20}$ +65.4

by Brown.[22] Thus, treatment of 2-bromobenzophenone (**11a**) and 2-bromo-4'-phenylbenzophenone (**11b**) with $LiAlH_4$ previously quenched with 2.5 equiv of (*R*)-(−)-2-(2-isoindolinyl)butan-1-ol (**12**) (Scheme 2) afforded (+)-**7h** and (+)-**7i** in ee > 93% (absolute stereochemistry not known).

When diethyl azodicarboxylate (DEAD) was added at 0 °C to a THF solution of CDI, Ph_3P, and an aliphatic primary or secondary alcohol **7**, the Mitsunobu reaction occurred readily to give the alkylated products **8** in moderate to good yields (Table 1). When diarylcarbinols (entries 10−15) were used as substrates an extended reaction time and excess reagents were required, but the transformations were highly efficient. The reaction proved unsuccessful when tertiary alcohols were used. Reactions carried out using a different phosphine (tributylphosphine) and/or inverting the order of reagents addition furnished similar results.

Enantiomerically pure aliphatic alcohols (−)-**7c**, (+)-**7c**, and (−)-**7d** (entries 4, 5, and 7) gave the corresponding 1-alkyl-4,5-dicyanoimidazoles (+)-**8c**, (−)-**8c**, and (+)-**8d** as single enantiomers (ee 97−98%), while diaryl alcohols (+)-**7h**−**i** afforded racemic products **8h,i**. However, when (*R*)-(+)-1-phenyl-1-propanol ((+)-**7e**) (entry 9) was tested, a 7:3 mixture of enantiomers of **8e** was obtained. In order to determine whether the partial racemization was due to the reaction itself or to the subsequent racemization of the chiral product, we quenched the reaction of (+)-**7e** 10 min after the addition of reagents. The product **8e** obtained after chromatographic separation showed the same ee as before (the same result was obtained when the reaction was run at −25 °C), suggesting that the racemization process may be due to the intrinsic mechanism of the reaction.[23] This result is in accord with those already observed by others in the Mitsunobu reaction of benzylic alcohols.[24]

Having secured a route to *N*-alkylimidazole derivatives **8**, we examined the hydrolysis−decarboxylation procedure (**8** to **10**, Scheme 1). For this purpose, the dicyanoimidazole derivatives **8c**−**g** (Table 2) were treated with 10 N NaOH in EtOH under reflux for 24 h, followed by acidification of the solution, to give the dicarboxylic acids **9c**−**g**. While decarboxylation of these acids using standard procedures[25] proved problematic, we found that a clean conversion of **9c**−**g** to **4** and **10c**−**f** could be performed in good yield by simply heating in diphenyl ether at reflux for 0.5 h. ^1H NMR analysis (*vide infra*) in the presence of chiral shift reagents showed ee values ≥97% for compounds (+)-**10c** and (+)-**10d**, revealing that no racemization had occurred during either of the final two steps. However, the hydrolysis−decarboxylation of (−)-**8e** resulted in formation of **10e** in racemic form. In order to establish which was the racemizing step, we analyzed the intermediate acid **9e** as its dimethyl ester (obtained from **9e** with excess CH_2N_2 in CH_2Cl_2). Since the ester showed an ee of 40% we conclude that **9e** racemizes during the decarboxylation process.

The enantiomeric excess (ee) of compounds (+)-**8c**, (−)-**8c**, (+)-**8d**, (−)-**8e**, (+)-**10c** was determined by 300-MHz ^1H NMR analysis in the presence of the chiral lanthanide shift reagent[26] europium(III) tris[3-((heptafluoropropyl)-hydroxymethylene)-(+)-camphorato][Eu(hfc)$_3$]. In the case of (+)-**10d**, europium(III) tris(*d,d*-dicampholylmethanate) was used. The spectra of pure (±)-**8d** and (+)-**8d** without and in the presence of Eu(hfc)$_3$ are reported in Figure 1. As shown, the resonances for the methyl, methylene, and imidazole protons are completely separated.

With the aim of avoiding the drastic conditions required for the hydrolysis−decarboxylation of dicyanoimidazole derivatives **8**, we used ethyl 4(5)-imidazolecarboxylate (**13**)[27] as the acidic reagent in the Mitsunobu reaction on alcohol **7g** (Scheme 3). The reaction was carried out under the same experimental conditions described above leading to a 3:1 mixture of regioisomers **14a** and **14b**, which could be separated by column chromatography.[28] The structure of these isomers was determined by ^1H and ^{13}C NMR and two-dimentional one bond ^1H−^{13}C correlation spectra. From these experiments it was possible to assign the benzhydryl and the imidazole methines, while long range ^1H−^{13}C correlation spectra were used to assign the position of the carbethoxy group on the imidazole ring. In the case of **14a** the benzhydryl proton showed a long range correlation with only one of the imidazole methines; on the other hand, for **14b** the correlation was found with both methines of the imidazole. These results indicate that the carbethoxy group is at position 5 in **14a** and at position 4 in **14b**.

The hydrolysis of compound **14a** was performed with LiOH in EtOH−water solution (0 °C, 2 h) to give the corresponding acid **15** in very good yield. Unfortunately, all attempts to decarboxylate this acid under mild conditions were unsuccessful; the previously described procedure was the only one which led to the imidazole derivative **4**.

It is worth noting that the conversion of **7g** (*via* **8g** and **9g**) into **4** represents a new preparation of bifonazole which compares favorably with other syntheses in terms of both overall yield (80%) and experimental requirements.

In conclusion, we have demonstrated that *N*-alkylimidazoles can be prepared in good overall yield through a three-step sequence starting from 4,5-dicyanoimidazole and alcohols. This procedure has a major advantage over more conventional routes (i.e., alcohol → alkyl halide → *N*-alkylimidazole) in that it allows the unprecedented

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(23) Other possibilities, such as rapid racemization of a chiral product during the reaction or the purification by silica gel chromatography, cannot be ruled out on the basis of these experiments.

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(28) When alcohol **7g** was converted into the bromide (Ph_3PBr_2) and then treated with **13** a 1:1 mixture of **14a** and **14b** was obtained in 32.5% overall yield.

Table 1. Mitsunobu Reaction of Alcohols 7 with 4,5-Dicyanoimidazole

entry[a]	substrate	R_1	R_2	config of **7** (ee, %)[b]	product (yield, %)[c]	config of **8** (ee, %)[b]
1	**7a**	H	H		**8a** (45)	
2	**7b**	H	n-C_7H_{15}		**8b** (98)	
3	(±)-**7c**	Me	n-C_6H_{13}		(±)-**8c** (70)	
4	(−)-**7c**	Me	n-C_6H_{13}	*R* (99)[d]	(+)-**8c** (65)	*S* (97)
5	(+)-**7c**	Me	n-C_6H_{13}	*S* (99)[d]	(−)-**8c** (67)	*R* (97)
6	(±)-**7d**	Me	Bn		(±)-**8d** (40)	
7	(−)-**7d**	Me	Bn	*R* (99)[d]	(+)-**8d** (39)	*S* (98)
8	(±)-**7e**	Et	Ph		(±)-**8e** (55)	
9	(+)-**7e**	Et	Ph	*R* (99)[d]	(−)-**8e** (55)	*S* (41)
10	**7f**	Ph	Ph		**8f** (94)	
11	(±)-**7g**	Ph	4-PhC_6H_4		(±)-**8g** (96)	
12	(±)-**7h**	Ph	2-BrC_6H_4		(±)-**8h** (81)	
13	(+)-**7h**	Ph	2-BrC_6H_4	ND[e]	(±)-**8h** (96)	*R,S* (0)
14	(±)-**7i**	2-BrC_6H_4	4-PhC_6H_4		(±)-**8i** (82)	
15	(+)-**7i**	2-BrC_6H_4	4-PhC_6H_4	ND (94)	(±)-**8i** (86)	*R,S* (0)

[a] All reactions were run at room temperature for 0.5 h with 1:1 ratio of reagents to substrate, except entries 10−15, run for 24 h with a reagents to substrate ratio of 4:1. [b] The enantiomeric excess was determined by 300-MHz ^{1}H NMR analysis in the presence of the chiral shift reagent Eu(hfc)$_3$. [c] Isolated yield based on the limiting alcohol used. [d] Commercially available. [e] ND = Absolute configuration not determined; compound (+)-**7h** showed $[\alpha]^{20}_D$ +44.8 (*c* 1.2, acetone) (lit.[22a] $[\alpha]^{20}_D$ +46.6 (*c* 1.3, acetone) corresponding to ee > 95%).

Table 2. Hydrolysis of 1-Alkyl-4,5-dicyanoimidazoles 8 to the Diacids 9 and Decarboxylation to 1-Alkylimidazoles 4 and 10c−f

entry	substrate	R_1	R_2	product **9** (yield, %)[a]	product **10** (yield, %)[a]	config of **10** (ee, %)[b]
1	(±)-**8c**	Me	n-C_6H_{13}	(±)-**9c** (77)	(±)-**10c** (81)	
2	(+)-**8c**	Me	n-C_6H_{13}	(+)-**9c**(65)	(+)-**10c** (77)	*S* (97)
3	(±)-**8d**	Me	Bn	(±)-**9d** (79)	(±)-**10d** (55)	
4	(+)-**8d**	Me	Bn	(+)-**9d** (76)	(+)-**10d** (53)	*S* (98)
5	(±)-**8e**	Et	Ph	(±)-**9e** (73)	(±)-**10e** (33)	
6	(−)-**8e**	Et	Ph	(-)-**9e** (73)	(±)-**10e** (38)	*R,S* (0)
7	**8f**	Ph	Ph	**9f** (97)	**10f** (90)	
8	(±)-**8g**	Ph	4-Ph-C_6H_4	(±)-**9g** (85)	(±)-**4** (98)	

[a] Isolated yields. [b] See footnote *b* in Table 1.

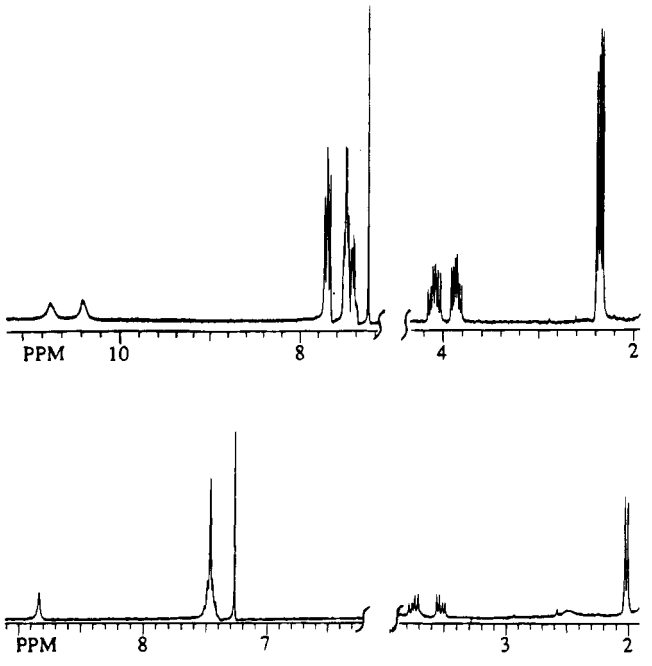
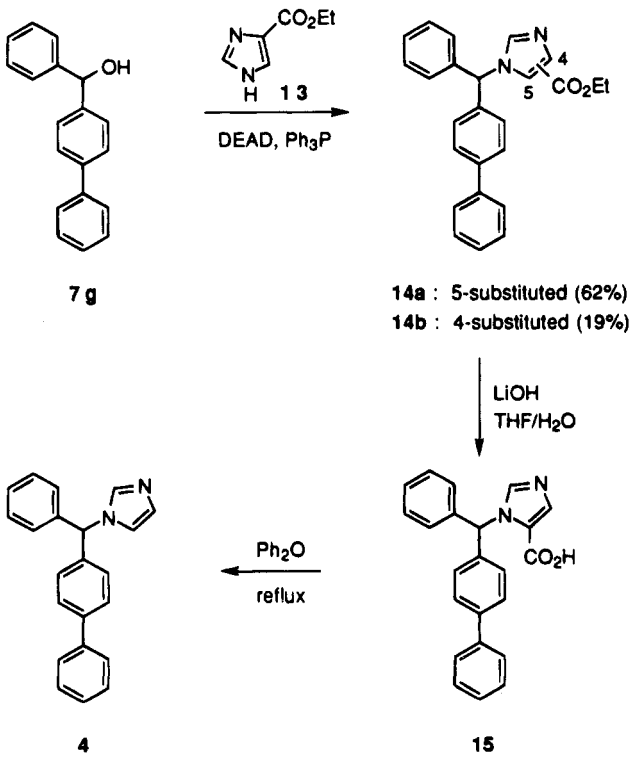


Figure 1. Selected signals of the ^{1}H NMR spectra (300 MHz) of (±)-**8d** (top) and (−)-**8d** (bottom) in the presence of europium(III) tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato][Eu(hfc)$_3$].

Scheme 3



synthesis of enantiomerically pure compounds from chiral aliphatic alcohols. In contrast, benzylimidazole derivatives racemize during the final step.

Marckwald Procedure. The rapid racemization of chiral benzyl alcohols during the Mitsunobu condensation with imidazole derivatives spurred us to seek an alternative route to enantiomerically pure 1-(1-phenylalkyl)-imidazole compounds. Several polysubstituted imidazoles have been obtained by constructing the heterocyclic ring starting from amines:[29] as a first attempt, we decided to follow the procedure recently reported by Cristalli[30]

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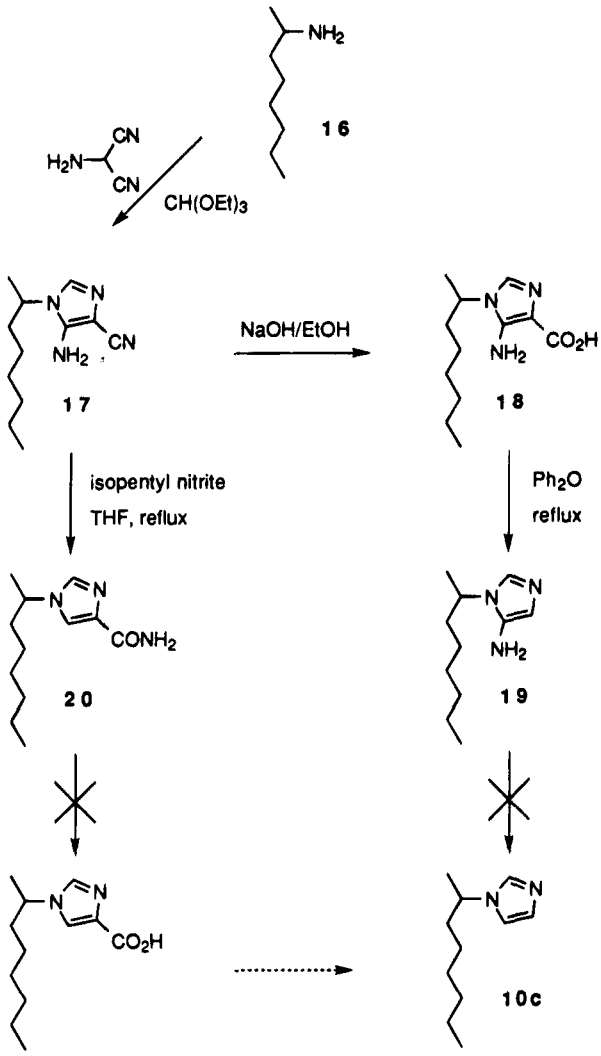
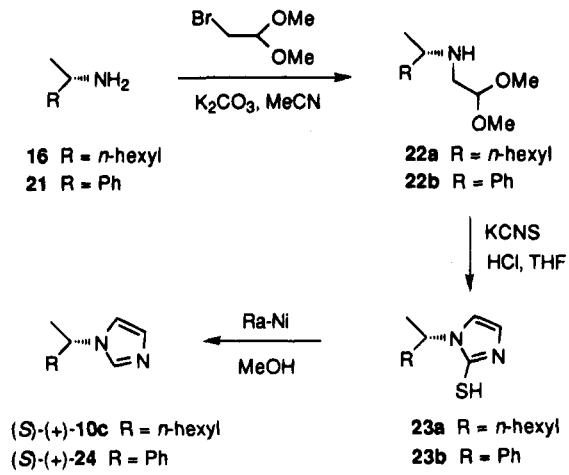
Scheme 4



for the preparation of *erythro*-1-(2-hydroxy-3-nonyl)-imidazole derivatives from *erythro*-3-amino-2-nonanol. Thus, when 2-octylamine (**16**) (Scheme 4) was treated with aminomalonitrile and triethyl orthoformate in CH_3CN, the imidazole derivative **17** was obtained in good yield.[31] However, although alkaline hydrolysis of **17** afforded the amino acid **18**, which was in turn decarboxylated to the aminoimidazole **19**, all attempts to deaminate **19** with $NaNO_2$–HCl or with isopentyl nitrite were unsuccessful. On the other hand, when **17** was reacted with isopentyl nitrite in THF, we were surprised to find that the amide **20** was obtained in 45% yield as the sole reaction product. Unfortunately, however, **20** could not be hydrolyzed to the corresponding acid under a variety of conditions.

Next we turned our attention to the method of imidazole synthesis sometimes referred to as the Marckwald procedure.[32] Treatment of (*S*)-(+)-2-octylamine (**16**)[18a] and (*S*)-(−)-α-methylbenzylamine (**21**) (Scheme 5) with bromoacetaldehyde dimethyl acetal provided the monoalkylated products **22a,b** in moderate to good yield as

Scheme 5



pale yellow oils, and these were cyclized to **23a,b** by reaction with KSCN and 3 N HCl in THF. Desulfuration with Ra-Ni afforded the final compounds (*S*)-(+)-**10c** and (S)-(+)-**24** in very good yield and with ee values higher than 98%. Compound (*S*)-(+)-**10c** so obtained was shown to be identical in all respects, including specific rotation, with (+)-**10c** derived from (*R*)-(−)-2-octanol (**7c**) *via* Mitsunobu–hydrolysis–decarboxylation sequence. It can therefore be inferred that, as expected, the Mitsunobu condensation proceeds with inversion of configuration of the starting alcohols.

Conclusions

We have reported in detail the synthesis of 1-alkylimidazoles through a three-step sequence involving the Mitsunobu reaction of alcohols with 4,5-dicyanoimidazole or ethyl 4(5)-imidazolecarboxylate, followed by hydrolysis and decarboxylation. This procedure has been successfully applied to a new, high yielding synthesis of the antifungal drug bifonazole. Chiral alcohols gave rise to enantiomerically pure 1-alkylimidazoles, with the exception of benzyl and benzhydryl alcohols, which led to racemic mixtures. It is interesting to point out that the Mitsunobu products are functionalized (chiral) imidazole derivatives that could be used as starting material for the preparation of differently substituted derivatives. Chiral 1-(phenylalkyl)imidazoles have been obtained by the Marckwald synthesis, and we believe this to be the first application of such a procedure to chiral amines.

Experimental Section

General Methods. Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra ($CHCl_3$ solutions unless otherwise stated) were recorded on a Perkin-Elmer 398 spectrophotometer. NMR spectra were run on Bruker AC 200 (200 MHz) or Varian XL 300 (300 MHz) spectrometers. ^1H NMR chemical shifts are reported relative to $CDCl_3$ at δ 7.24 ppm and tetramethylsilane at δ 0.00 ppm. EI low-resolution mass spectra were recorded on a Kratos MS 80 spectrometer with an electron beam of 70 eV. Elemental analyses (C, H, N) were performed in house on a Perkin-Elmer 240C analyzer.

Anhydrous DMF was purchased from Aldrich Chemical Co. THF was distilled from potassium benzophenone ketyl. CH_3CN was distilled from P_2O_5. Reagents were from commercial suppliers and used without further purification. Extracts were dried over Na_2SO_4 and evaporated under reduced pressure with a rotary evaporator. Merck silica gel 60 was used for

(30) Cristalli, G.; Eleuteri, A.; Franchetti, P.; Grifantini, M.; Vittori, S.; Lupidi, G. *J. Med. Chem.* **1991**, *34*, 1187.
(31) When (*S*)-(+)-2-octylamine was used under the same conditions, chiral **17** was obtained in 52% yield and in 98% ee.
(32) Wohl, A.; Marckwald, W. *Ber.* **1892**, *25*, 2354.
(33) *The Merck Index*, 11th ed.; Merck & Co., Inc.: Rahway, NJ, 1989; p 189.

chromatography (70–230 mesh) and flash chromatography (230–400 mesh) columns. The plates used for analytical and preparative TLC were Merck silica gel 60 F_{254} (0.2 mm and 2 mm thickness, respectively). Yields of the reactions refer to the purified products and are not optimized.

General Procedure for the Mitsunobu Reaction. Method a. DEAD (1 mL, 6.0 mmol) was added dropwise to a cooled (0 °C) solution of alcohol **7** (6.0 mmol), Ph_3P (1.57 g, 6.0 mmol), and DCI (0.71 g, 6.0 mmol) in 60 mL of dry THF. The mixture was stirred for 0.5 h at rt, the solvent was removed, and the residue was treated with hexanes/Et_2O (1:1). The solution was filtered, and the precipitate was washed with hexanes. Evaporation of the combined filtrates afforded a crude product which was purified as described below. **Method b.** The reaction was carried out by adding 1 equiv of all the reagents to alcohol **7** at 45 min intervals. After four additions of reagents, the reaction mixture was allowed to stir at room temperature for 24 h and then treated as above.

For yields, absolute configuration, and percent ee of the products, see Table 1.

1-Methylimidazole-4,5-dicarbonitrile (8a) (Method a). Purified by chromatography (AcOEt) and then recrystallized from CH_2Cl_2/hexane: white solid; mp 96–98 °C; IR 2260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 (s, 3H), 7.70 (s, 1H). Anal. Calcd for $C_6H_4N_4$: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.70; H, 3.00; N, 42.30.

1-(*n*-Octyl)imidazole-4,5-dicarbonitrile (8b) (Method a). Purified by flash chromatography (AcOEt): colorless oil; IR 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 5 Hz, 3H), 1.66 (m, 10H), 1.93 (q, J = 5 Hz, 2H), 4.18 (t, J = 6 Hz, 2H), 7.69 (s, 1H). Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 68.08; H, 7.73; N, 24.19.

(*R,S*)-1-(2-Octyl)imidazole-4,5-dicarbonitrile [(±)-8c] (Method a). Purified by preparative TLC (hexanes/AcOEt 3:1): colorless oil; IR 2240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 5.7 Hz, 3H), 1.28 (m, 8H), 1.65 (d, J = 5.7 Hz, 3H), 1.93 (m, 2H), 4.43 (sextet, J = 5.7 Hz, 1H), 7.75 (s, 1H). Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.92; H, 7.93, N, 24.15.

(*S*)-(+)-1-(2-Octyl)imidazole-4,5-dicarbonitrile [(+)-8c] (method a): $[\alpha]^{20}_{546}$ +1.1 (*c* 2.91, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**8c**.

(*R*)-(−)-1-(2-Octyl)imidazole-4,5-dicarbonitrile [(−)-8c] (Method a): $[\alpha]^{20}_{546}$ −1.0 (*c* 2.18, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**8c**.

(*R,S*)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarbonitrile [(±)-8d] (Method a). Purified by flash chromatography (hexanes/AcOEt 3:1 as eluent). An analytical sample was prepared by recrystallization from benzene/cyclohexane: white solid; mp 138–140 °C; IR 2240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 4.3 Hz, 3H), 2.86 (dd, J = 14.1, 4.3 Hz, 2H), 2.93 (dd, J = 14.1, 4.3 Hz, 2H), 4.38 (sextet, J = 4.3 Hz, 1H), 6.83 (m, 2H), 7.05 (m, 3H), 7.26 (s, 1H). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.33; H, 5.01; N, 23.57.

(*S*)-(+)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarbonitrile [(+)-8d] (Method a): $[\alpha]^{20}_{D}$ +58.8 (*c* 0.85, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**8d**.

(*R,S*)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarbonitrile [(±)-8e] (Method a). Purified by flash chromatography (hexanes/AcOEt 2:1 as eluent). An analytical sample was obtained by preparative TLC: colorless oil; IR 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (t, J = 7.4 Hz, 3H), 2.38 (quintet, J = 7.4 Hz, 2H), 5.23 (t, J = 7.4 Hz, 1H), 7.28 (m, 2H), 7.38 (m, 3H), 7.88 (s, 1H). Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.38; H, 5.20; N, 23.42.

(*S*)-(−)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarbonitrile [(−)-8e] (method a): $[\alpha]^{20}_{D}$ −44.3 (*c* 2.82, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**8e**.

1-(α-Phenylbenzyl)imidazole-4,5-dicarbonitrile (8f) (Method b). Purified by flash chromatography (hexanes/AcOEt 2:1) followed by recrystallization from Et_2O: white solid; mp 137–138 °C; IR 2250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.70 (s, 1H), 7.13 (m, 4H), 7.43 (m, 7H). Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.24; H, 4.18; N, 19.58.

1-[α-(4-Biphenylyl)benzyl]imidazole-4,5-dicarbonitrile (8g) (Method b). Purified by flash chromatography (hexanes/AcOEt 5:1–3:1). An analytical sample was prepared by recrystallization from Et_2O: white solid; mp 58–59 °C; IR 2225 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.74 (s, 1H), 7.45 (m, 4H), 7.6 (m, 11H). Anal. Calcd for $C_{24}H_{16}N_4$: C, 79.98; H, 4.47; N, 15.54. Found: C, 80.12; H, 4.39; N, 15.49.

(*R,S*)-1-[α-(2-Bromophenyl)benzyl]imidazole-4,5-dicarbonitrile [(±)-8h] (Method b). Purified by flash chromatography (hexanes/AcOEt 2:1 as eluent) followed by recrystallization from methanol: white solid; mp 176–177 °C; IR 2240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.82 (dd, J = 5.7, 2.0 Hz, 1H), 7.05 (s, 1H), 7.10 (m, 2H), 7.38 (m, 3H), 7.45 (m, 3H), 7.70 (dd, J = 5.7, 2.0 Hz, 1H). Anal. Calcd for $C_{18}H_{11}BrN_4$: C, 59.52; H, 3.05; N, 15.43. Found: C, 59.43; H, 3.12; N, 15.58.

(*R,S*)-1-[α-(2-Bromophenyl)-4-phenylbenzyl]imidazole-4,5-dicarbonitrile [(±)-8i] (Method b). Purified by flash chromatography (hexanes/AcOEt 3:1 as eluent) followed by recrystallization from MeOH: white solid; mp 169–171 °C; IR 2220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.89 (dd, J = 6.0, 1.8 Hz, 1H), 7.06 (s, 1H), 7.14 (d, J = 7.0 Hz, 2H), 7.41 (m, 6H), 7.65 (m, 5H). Anal. Calcd for $C_{24}H_{15}BrN_4$: C, 65.62; H, 3.44; N, 12.75. Found: C, 65.80; H, 3.33; N, 12.91.

General Procedure for the Hydrolysis of 8 to the Diacids 9. A solution of **8** (10 mmol) in 30 mL of EtOH was refluxed for 24 h in the presence of 10 M NaOH (30 mL, 0.30 mol). The hot solution was poured into 150 mL of cold water, filtered, and brought to pH 2 with 37% HCl. After cooling, the precipitate was filtered, washed with EtOH and then with Et_2O, and dried. For yields, absolute configuration, and percent ee of the products, see Table 2.

(*R,S*)-1-(2-Octyl)imidazole-4,5-dicarboxylic Acid [(±)-9c]. Recrystallized from EtOH: white solid; mp 188–190 °C; IR 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, J = 6.0 Hz, 3H), 1.28 (m, 8H), 1.70 (d, J = 6.0 Hz, 3H), 1.90 (m, 2H), 5.93 (m, 1H), 8.68 (s, 1H). Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.31; H, 7.58; N, 10.29.

(*S*)-(+)-1-(2-Octyl)imidazole-4,5-dicarboxylic acid [(+)-9c]: $[\alpha]^{20}_{D}$ +20.0 (*c* 0.95, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**9c**.

(*R,S*)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarboxylic Acid [(±)-9d]. Recrystallized from EtOH: mp 210–212 °C; IR (Nujol mull) 1735 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.51 (d, J = 6.9 Hz, 3H), 3.10 (dd, J = 13.1, 6.7 Hz, 1H), 3.25 (dd, J = 13.1, 6.7 Hz, 1H), 6.07 (sextet, J = 6.9 Hz, 1H), 7.23 (m, 5H), 9.36 (s, 1H). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.44; H, 5.27; N, 9.98.

(*S*)-(+)-1-(1-Phenyl-2-propyl)imidazole-4,5-dicarboxylic acid [(+)-9d]: $[\alpha]^{20}_{D}$ +2.0 (*c* 1.40, C_6H_5N). Physical and spectral data were identical with those described above for the racemate (±)-**9d**.

(*R,S*)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarboxylic Acid [(±)-9e]. Recrystallized from EtOH/H_2O (7:3): mp 180–182 °C; IR 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (t, J = 6.8 Hz, 3H), 2.34 (quintet, J = 6.8 Hz, 2H), 6.83 (t, J = 6.8 Hz, 1H), 7.42 (s, 5H), 8.65 (s, 1H). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.51; H, 5.00; N, 10.06.

(*S*)-(−)-1-(1-Phenyl-1-propyl)imidazole-4,5-dicarboxylic acid [(−)-9e]: $[\alpha]^{25}_{365}$ −72.8 (*c* 2.80, DMF). Physical and spectral data were identical with those described above for the racemate (±)-**9e**.

1-(α-Phenylbenzyl)imidazole-4,5-dicarboxylic Acid (9f). Recrystallized from EtOH; mp 202–204 °C; IR (nujol mull) 1730 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.15 (m, 4H), 7.46 (m, 6H), 8.10 (s, 1H), 8.56 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.30; H, 4.49; N, 8.50.

(*R,S*)-1-[α-(4-Biphenylyl)benzyl]imidazole-4,5-dicarboxylic Acid [(±)-9g]. Recrystallized from EtOH (70%)/DMF (98:2): mp 211–213 °C; IR (Nujol mull) 1740 cm^{-1}; ^1H NMR (200 MHz, DMF-d_7) δ 7.45 (m, 10H), 7.85 (m, 4H), 8.41 (s, 1H),

8.95 (s, 1H). Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.61; H, 4.38; N, 6.88.

General Procedure for the Decarboxylation of 9 to 1-Alkylimidazoles 4 and 10. A solution of **9** (10 mmol) in 20 mL of diphenyl ether was heated at reflux for 0.5 h and, after cooling, applied to a silica gel column. Elution with Et_2O eliminated the excess diphenyl ether, and further elution with AcOEt gave the products, which were further purified by preparative TLC (AcOEt for **10c** and **10d**, $CHCl_3$/MeOH 98:2 for **10e**) or recrystallization (for **10f** and **4**). For yields, absolute configuration, and percent ee of the products, see Table 2.

***(R,S)*-1-(2-Octyl)imidazole [(±)-10c]:** oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.76 (t, J = 7.0 Hz, 3H), 1.19 (br s, 8H), 1.41 (d, J = 7.0 Hz, 3H), 1.65 (q, J = 7.0 Hz, 2H), 4.04 (sextet, J = 7.0 Hz, 1H), 6.82 (s, 1H), 6.97 (s, 1H), 7.38 (s, 1H). Anal. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.48; H, 11.26; N, 15.26.

***(S)*-(+)-1-(2-Octyl)imidazole [(+)-10c]:** $[\alpha]^{20}_D$ +16.0 (*c* 1.1, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**10c**.

1-(1-Phenyl-2-propyl)imidazole [(±)-10d]: oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (d, J = 7.0 Hz, 3H), 2.92 (d, J = 7.0 Hz, 2H), 4.30 (sextet, J = 7.0 Hz, 1H), 6.93 (m, 4H), 7.17 (m, 4H). Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.51; H, 7.67; N, 14.82.

***(S)*-(+)-1-(1-Phenyl-2-propyl)imidazole [(+)-10d]:** $[\alpha]^{20}_D$ +93.3 (*c* 0.75, $CHCl_3$). Physical and spectral data were identical with those described above for the racemate (±)-**10d**.

***(R,S)*-1-(1-Phenyl-1-propyl)imidazole [(±)-10e]:** oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (t, J = 7.0 Hz, 3H), 2.23 (m, 2H), 5.00 (t, J = 7.0 Hz, 1H), 6.94 (s, 1H), 7.07 (s, 1H), 7.16 (m, 2H), 7.36 (m, 3H), 7.59 (s, 1H). Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.48; H, 7.49; N, 15.03. Starting from (*S*)-(−)-**9e** the same racemic compound (±)-**10e** was obtained.

1-(α-Phenylbenzyl)imidazole (10f): white crystals; mp 88−89 °C (CH_3CN); ^1H NMR (200 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.85 (s, 1H), 7.08 (m, 5H), 7.36 (m, 7H). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.89; H, 5.95; N, 12.16.

***(R,S)*-1-[α-(4-Biphenylyl)benzyl]imidazole [bifonazole, (±)-4]:** white crystals; mp 145−147 °C (EtOH) (lit.[32] mp 142 °C, from CH_3CN); ^1H NMR (200 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.88 (s, 1H), 7.13 (m, 10H), 7.42 (m, 6H). Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.84; N, 9.03. Found: C, 85.21; H, 5.80; N, 8.99.

Following the same procedure **4** was also obtained in 94% yield by decarboxylation of **15**.

(+)-2-Bromo-4′-phenylbenzhydrol [(+)-7i]. Prepared as follows according to Brown and co-workers.[22a] To a 1 M solution of $LiAlH_4$ in Et_2O (30 mL, 30 mmol) was added a solution of (*R*)-(−)-2-(2-isoindolinyl)butan-1-ol (**12**) (14.32 g, 75 mmol) in 200 mL of Et_2O dropwise in 3 h at rt. After 45 min, the mixture was cooled to −15 °C, and a solution of 2-bromo-4′-phenylbenzophenone (**11b**)[34] (8.43 g, 25 mmol) in 30 mL of Et_2O was slowly added during 2 h under stirring. After a further 15 min, the reaction mixture was quenched with 1 N NaOH (20 mL). The organic phase was washed successively with 1 N HCl (2 × 100 mL) and 1 N NaOH (2 × 100 mL) and then with water until neutral. Concentration of the dried extracts afforded a crude oil, which was purified by flash chromatography ($CHCl_3$/hexanes 8:2) to give the title compound: white crystals; mp 101−103 (cyclohexane); $[\alpha]^{20}_D$ +65.4 (*c* 2.60, $CHCl_3$); IR 3120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 1H), 6.24 (s, 1H), 7.48 (m, 13H). Anal. Calcd for $C_{19}H_{15}BrO$: C, 67.27; H, 4.46. Found: C, 67.35; H, 4.40.

Ethyl 1-[α-(4-Biphenylyl)benzyl]imidazole-5-carboxylate (14a) and Ethyl 1-[α-(4-Biphenylyl)benzyl]imidazole-4-carboxylate (14b). Prepared by Mitsunobu coupling of alcohol **7g** and ethyl 4(5)-imidazolecarboxylate (**13**)[27] as the acidic reagent, following the same procedure (method b) described for (±)-**8i**. After preliminary purification by flash chromatography (hexanes/AcOEt 3:1), the isomer mixture was separated by a second chromatography using the same eluent affording the less polar compound (R_f 0.66), which was assigned the structure **14a**. The second eluted isomer **14b** (R_f 0.22) was further purified by flash chromatography using gradient elution with hexanes/AcOEt 3:1−1:1.

14a: 50% yield; mp 136−137 °C (EtOH); IR cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 7.13 (m, 4H), 7.36 (m, 7H), 7.58 (m, 5H), 7.85 (s, 1H). Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.33. Found: C, 78.70; H, 5.75; N, 7.24.

14b: 16% yield; mp 149−151 °C (EtOH); IR cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (t, J = 6.9 Hz, 3H), 4.34 (q, J = 6.9 Hz, 2H), 6.58 (s, 1H), 7.16 (m, 4H), 7.54 (m, 12H). Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.33. Found: C, 78.73; H, 5.84; N, 7.19.

1-[α-(4-Biphenylyl)benzyl]imidazole-5-carboxylic Acid (15). Aqueous 10% LiOH (1 mL, 4.2 mmol) was added to a solution of **14a** (0.110 g, 0.29 mmol) in 4 mL of EtOH. After being stirred for 2 h, the reaction mixture was cooled to 0 °C and acidified by addition of 1 N HCl. The white precipitate was stirred at the same temperature for 30 min and then filtered to give pure **15** (0.098 g, 96%) as white crystals: mp 163−166 °C (EtOH/H_2O); IR (Nujol mull) 1740 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.41 (m, 4H), 7.62 (m, 6H), 7.69 (m, 7H). Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.91. Found: C, 78.12; H, 5.19; N, 7.83.

Synthesis of 5-Amino-1-(2-octyl)imidazole (19) from 2-Octylamine (16). Dry NH_3 was bubbled for 30 min through a stirred suspension of aminomalonitrile *p*-toluenesulfonate (3.9 g, 15.5 mmol) in dry CH_3CN (200 mL). After the solid that separated was filtered, the solution was concentrated to 100 mL and then added to triethyl orthoformate (2.6 mL, 15.5 mmol). The solution was heated under reflux for 15 min. To the cooled mixture was added 2-octylamine (**16**) (2.6 mL, 15.5 mmol), and the solution was stirred at rt overnight. The solvent was evaporated, and the residue was purified by flash chromatography (AcOEt/hexanes 3:2) to give a yellow semisolid product, which after treatment with Et_2O/hexanes afforded 5-amino-1-(2-octyl)imidazole-4-carbonitrile (**17**) (1.8 g, 53%) as a white crystalline compound: mp 110 °C (cyclohexane); IR 3360, 2240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 6.5 Hz, 3H), 1.26 (br s, 8H), 1.46 (d, J = 6.7 Hz, 3H), 1.75 (m, 2H), 3.96 (m, 1H), 7.13 (s, 1H). Anal. Calcd for $C_{12}H_{20}N_4$: C, 65.41; H, 9.15; N, 25.44. Found: C, 65.67; H, 9.08; N, 25.25.

A mixture of **17** (0.30 g, 1.36 mmol), EtOH (3 mL), and aqueous 10 N NaOH (3 mL) was heated under reflux for 24 h. The solution was cooled to rt and diluted with water (2 mL), and 2 N HCl was slowly added until neutrality. After 2 h in a cool place, the precipitate was filtered and washed with water to give 5-amino-1-(2-octyl)imidazole-4-carboxylic acid (**18**) (0.32 g, 115%) as a chromatographically pure (5% AcOH in AcOEt, R_f 0.58), white crystalline solid with no defined mp and containing some water of crystallization: IR (Nujol mull) 3350, 1735 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6 + D_2O) δ 0.84 (t, J = 7.3 Hz, 3H), 1.25 (br s, 8H), 1.37 (d, J = 7.4 Hz, 3H), 1.73 (m, 2H), 4.11 (m, 1H), 7.18 (s, 1H). **18** was not further purified and was used directly in the next step.

The acid **18** was decarboxylated following the same procedure described for acids **9** affording 5-amino-1-(2-octyl)imidazole (**19**) in 15% yield: colorless oil; IR 3350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + D_2O) δ 0.88 (t, J = 6.8 Hz, 3H), 1.30 (br s, 8H), 1.48 (d, J = 7.0 Hz, 3H), 1.75 (m, 2H), 4.04 (m, J = 7.2 Hz, 1H), 4.75 (s, 1H), 7.21 (s, 1H). Anal. Calcd for $C_{11}H_{21}N_3$: C, 67.64; H, 10.84; N, 21.52. Found: C, 67.80; H, 10.72; N, 21.35.

1-(2-Octyl)imidazole-4-carboxamide (20). A solution of **17** (0.33 g, 1.5 mmol) in 10 mL of THF was added during 1 h to a refluxing solution of isoamyl nitrite (0.63 mL, 4.5 mmol) in 5 mL of THF. After being heated under reflux for 1 h, the reaction mixture was cooled, concentrated, and purified by flash chromatography (2.5% Et_3N in AcOEt, R_f 0.45) to provide **20** (0.19 g, 45%) as a white amorphous powder with no defined mp: IR 3540, 3420, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + D_2O) δ 0.86 (t, J = 6.7 Hz, 3H), 1.32 (m, 8H), 1.49 (d, J = 6.8 Hz, 3H), 1.75 (m, 2H), 4.17 (m, 1H), 7.59 (s, 1H), 7.67 (s, 1H).

(34) Prepared by Friedel−Crafts acylation of 4-biphenyl following the standard procedure, mp 97−99 °C (Et_2O).

Anal. Calcd for $C_{12}H_{21}N_3O$: C, 64.51; H, 9.51; N, 18.81. Found: C, 64.84; H, 9.30; N, 18.48.

General Procedure for the Synthesis of *N*-(2,2-Dimethoxyethyl)amines 22a and 22b. To a solution of (*S*)-(+)-2-octylamine (**16**)[18a] and (*S*)-(−)-α-methylbenzylamine (**21**) (4.0 mmol) in 30 mL of CH_3CN were added anhydrous K_2CO_3 (0.83 g, 6.0 mmol) and bromoacetaldehyde dimethyl acetal (0.68 g, 4.0 mmol), and the reaction mixture was heated under reflux for 48 h. After cooling, the inorganic salts were removed by filtration and the solution was evaporated under reduced pressure. The residue was purified by column chromatography (AcOEt) to give **22a** and **22b** as yellow oils which were used without further purification.

22a: 62% yield; no specific rotation could be measured at different wavelengths; IR 3340 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6.3 Hz, 3H), 1.04 (d, J = 6.2 Hz, 3H), 1.27 (m, 8H), 2.05 (s, 1H), 2.72 (m, 4H), 3.85 (s, 6H), 4.65 (t, J = 6.2 Hz, 1H).

22b: 70% yield; $[\alpha]^{20}_D$ -31.0 (*c* 2.09, $CHCl_3$); IR 3345 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (d, J = 6.5 Hz, 3H), 1.65 (s, 1H, exchangeable with D_2O), 2.55 (dd, J = 12.1, 6.3 Hz, 1H), 2.65 (dd, J = 12.1, 6.3 Hz, 1H), 3.29 (s, 3H), 3.34 (s, 3H), 3.76 (q, J = 6.5 Hz, 1H), 4.45 (t, J = 6.5 Hz, 1H), 7.35 (m, 5H).

General Procedure for the Synthesis of 23a and 23b. To a solution of **22a** or **22b** (2.0 mmol) in 50 mL of THF were added 3 N HCl (0.8 mL, 2.4 mmol) and KSCN (0.23 g, 2.4 mmol). After being stirred at 70 °C for 8 h, the cooled solution was basified by addition of 1 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with brine and then dried and evaporated. The residue was purified by column chromatography (AcOEt) to give pure **23a** and **23b**.

23a: 84% yield; mp 84−85 °C (Et_2O). $[\alpha]^{20}_D$ -35.6 (*c* 0.45, $CHCl_3$); IR 2580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H), 1.25 (m, 8H), 1.33 (d, J = 7.0 Hz, 3H), 1.70 (m, 2H), 4.92 (m, J = 7.0 Hz, 1H), 6.69 (s, 1H), 6.75 (s, 1H), 11.40 (br s, 1H, exchangeable with D_2O). Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.21; H, 9.49; N, 13.19. Found: C, 62.41; H, 9.53; N, 13.25.

23b: 84% yield; mp 124−127 °C (Et_2O); $[\alpha]^{20}_D$ −239.2 (*c* 4.10, $CHCl_3$); IR 2585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.74 (d, J = 7.4 Hz, 3H), 6.20 (q, J = 7.4 Hz, 1H), 6.58 (s, 1H), 6.70 (s, 1H), 7.32 (m, 5H), 11.93 (br s, 1H, exchangeable with D_2O). Anal. Calcd for $C_{11}H_{12}N_2S$: C, 64.66; H, 5.92; N, 13.72. Found: C, 64.52; H, 5.88; N, 13.80.

General Procedure for the Hydrogenolysis of 23a and 23b. Excess Ra-Ni (50% slurry in water) was added to a solution of **23a** or **23b** (2.0 mmol) in 10 mL of MeOH. The flask was immersed in an oil bath preheated to 100 °C and after 5 min cooled to rt. The reaction mixture was filtered through Celite, and the filtrate was diluted with $CHCl_3$, washed with brine, and dried. Evaporation of the solvent afforded a residue which was purified by column chromatography (5% MeOH in AcOEt) to give (+)-**10c** (85% yield) (identical in all the respects to that obtained by decarboxylation of (+)-**9c**) and (*S*)-(+)-**24** (quantitative yield): yellow oil; $[\alpha]^{20}_D$ +5.20 (*c* 3.84, $CHCl_3$); ee > 98%; ^1H NMR (200 MHz, $CDCl_3$) δ 1.87 (d, J = 8.0 Hz, 3H), 5.34 (q, J = 8.0 Hz, 1H), 6.90 (s, 1H), 7.08 (s, 1H), 7.14 (m, 2H), 7.30 (m, 3H), 7.58 (s, 1H). Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.03; N, 16.27. Found: C, 76.86; H, 7.10; N, 16.04.

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