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# An Approach to Primary Allylic Amines via Transition-Metal-Catalyzed Reactions. Total Synthesis of (±)-Gabaculine

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The reaction of allylic acetates with 4,4'-dimethoxybenzhydrylamine catalyzed by tetrakis(triphenylphosphine)palladium yields the *E*-allylated 4,4'-dimethoxybenzhydrylamines regardless of the initial olefin geometry. Good regiochemical control for reaction at the less substituted end of the allyl unit regardless of the regioisomer of the starting allylic acetate is obtained. Removal of the 4,4'-dimethoxybenzhydryl group is nicely accomplished by formolysis to give the primary allyl amines. A regiocontrolled synthesis of the naturally occurring amino acid (±)-gabaculine in 45% overall yield from 3-cyclohexenecarboxylic acid is reported utilizing this key amination procedure.

The preparation of primary amines normally entails the use of ammonia equivalents such as phthalimides (Gabriel synthesis),[1] bis(sulfenyl) amides (Mukaiyama synthesis),[2] phosphoramides,[3] or trifluoroacetamides.[4] Such approaches frequently have drawbacks. The nitrogen must be deprotonated to make it sufficiently nucleophilic for reaction. In the case of the *N*-alkylphthalimides, rather harsh hydrolysis conditions must be employed to remove the protecting group.[5] Recently, a quite interesting method employing hydroxylamines was reported by Mukaiyama.[6] The tremendous importance of alkylamines continues to provide the impetus to evolve mild methods for their synthesis.

Reaction of either preformed $\pi$-allylpalladium complexes[7,8] or such complexes formed in situ with alkylamines[7,9] is known to proceed under mild conditions. Attempts to extend the catalytic in situ method to the synthesis of primary amines by use of ammonia failed. In order to circumvent the inability to use ammonia, we turned our attention to an alkylated amine in which the alkyl group could be easily removed. We report the successful development of such an approach and its application to the regiocontrolled synthesis of (±)-gabaculine,[10,11,18] a fascinating naturally occurring amino acid which inhibits the enzyme $\gamma$-aminobutyrate aminotransferase.

Table I. $^{13}$C NMR Data

| | δ (vinyl carbons) | | | | |
|---|---|---|---|---|---|
| | a | b | c | d | δ($CH_3$) |
| **A. Sorbyl Systems** | | | | | |
| sorbyl acetate | 123.7 | 130.5 | 131.0 | 134.8 | 18.1 |
| **3** | 128.3 | 129.3 | 131.2 | 131.6 | 17.9 |
| **4** | 127.9 | 128.3 | 131.4 | 132.8 | 17.9 |
| **B. Geranyl-Neryl Systems** | | | | | |
| geranyl acetate | 118.9 | 141.8 | 16.4 | 39.5 | |
| | 119.7 | 142.1 | 23.5 | 31.3 | |
| neryl acetate | 123.0 | 137.7 | 16.2 | 39.6 | |
| **13** | | | | | |

## Results

The approach employed the catalytic in situ generation of $\pi$-allylpalladium cationic complexes by reacting allylic

(1) S. Gabriel, *Chem. Ber.*, **20**, 2224 (1887); M. S. Gibson and R. W. Bradshaw, *Angew. Chem., Int. Ed. Engl.*, **7**, 919 (1968).
(2) T. Mukaiyama, T. Taguchi, and M. Nishi, *Bull. Chem. Soc. Jpn.*, **44**, 2797 (1971).
(3) A. Zwierzak and J. Brylikowska-Piotrowicz, *Angew. Chem., Int. Ed. Engl.*, **16**, 107 (1977). Also see A. Jonczyk, Z. Ochal, and M. Makosza, *Synthesis*, 882 (1978).
(4) J. E. Nordlander, D. B. Catalane, T. H. Eberlein, L. V. Farkas, R. S. Howe, R. M. Stevens, N. A. Tripoulas, R. E. Stansfield, J. L. Cox, M. J. Payne, and A. Viehbeck, *Tetrahedron Lett.*, 4987 (1978).
(5) S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, **97**, 5582 (1975).
(6) T. Mukaiyama, T. Tsuji, and Y. Watanabe, *Chem. Lett.*, 1057 (1978).
(7) For a review see B. M. Trost, *Tetrahedron*, **33**, 2615 (1977).
(8) B. Akermark and K. Zetterberg, *Tetrahedron Lett.*, 3733 (1975).
(9) B. M. Trost and J. P. Genet, *J. Am. Chem. Soc.*, **98**, 8516 (1976); K. Takahasi, A. Miyake, and G. Hata, *Bull. Chem. Soc. Jpn.*, **45**, 230 (1972); K. E. Atkins, W. E. Walker, and R. M. Manyik, *Tetrahedron Lett.*, 3821 (1970).
(10) K. Kobayashi, S. Miyazawa, A. Terahara, H. Mishima, and H. Kurihara, *Tetrahedron Lett.*, 537 (1976).
(11) For a recent unsuccessful approach, see S. Danishefsky and F. M. Hershenson, *J. Org. Chem.*, **44**, 1180 (1979).

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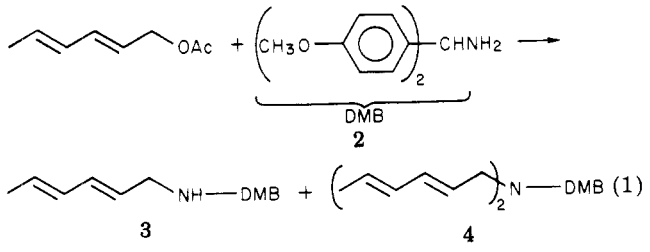
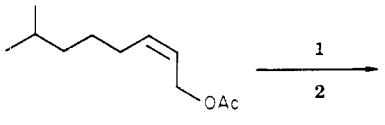
acetates with tetrakis(triphenylphosphine)palladium (1). While benzylamine can be used with excellent yields in the alkylation, the requirement of catalytic hydrogenolysis for a mild method to remove the benzyl substituent (which might lead to a problem in chemoselectivity for allylic amines) led us to use a benzhydrylamine which could be removed under mild acid conditions. Treatment of sorbyl acetate with 4,4'-dimethoxybenzhydrylamine (2)[12,13] in the presence of 3–5 mol % of 1 in refluxing THF led to a 62% yield of the desired alkylated amine 3 in addition to 19% of the dialkylated product 4 (eq 1, DMB = 4,4'-dimethoxybenzhydryl). This corresponds to a mole ratio for 3:4



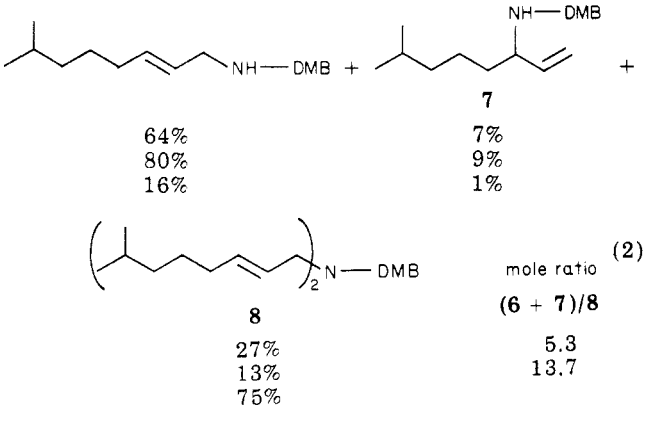

3 4

of 6.5. Use of the polymerically supported catalyst[14] led to a slight improvement in the mole ratio of 3:4 to 8.8. A greatly improved yield (quantitative) and selectivity (mole ratio of 3:4 10.6) is obtained by performing the reaction at room temperature with an excess of 2. The regio- and stereohomogeneity is established by the $^{13}C$ and $^{1}H$ NMR spectra (see Experimental Section). The $^{13}C$ spectra also support the *E,E* configuration. As summarized in Table IA, the close agreement of the shifts for the vinyl carbons and the methyl group of the sorbyl unit to those in (*E,E*)-sorbyl acetate indicates the same stereochemical arrangement.

The formation of a single olefin isomer from sorbyl acetate may be the result of either kinetic or thermodynamic control. To examine this question, we employed the *Z*-olefin 5[15] (eq 2). Again, monoalkylation is best achieved




5 1.2 equiv of 2, reflux
2.0 equiv of 2, room temp
0.45 equiv of 2, reflux

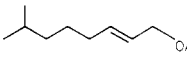
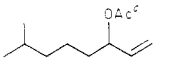



(12) Cf. R. W. Hanson and H. D. Law, *J. Chem. Soc.*, 7285 (1965), who used 4,4'-dimethoxybenzhydryl as a protecting group for the nitrogen of amino acids.

(13) H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969). These authors report only the picrate salt of amine 2.

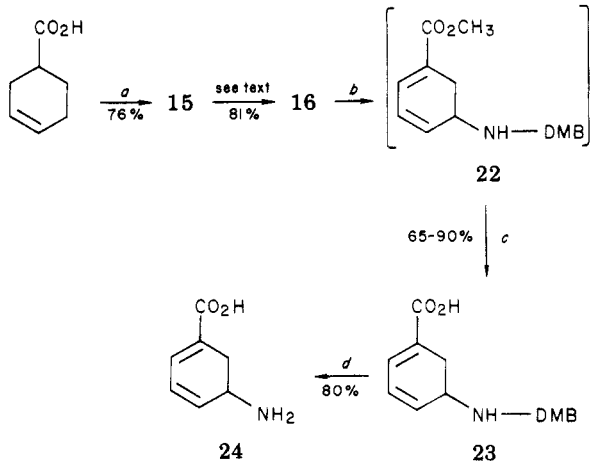
(14) B. M. Trost and E. Keinan, *J. Am. Chem. Soc.*, **100**, 7779 (1978).

Table II. Isomerization of 5 during Alkylation

| | time, min | % 5[c] |  |  |
|---|---|---|---|---|
| A[a] | 0 | 100 | 0 | 0 |
| | 10 | 8 | 33 | 22 |
| | 25 | 2 | 17 | 13 |
| | 40 | 1 | 11 | 8 |
| | 60 | | 5 | 4 |
| | 80 | | 2 | 1.5 |
| | 120 | | | |
| B[b] | 0 | 100 | | |
| | 20 | 29 | 4 | 3 |
| | 35 | 15 | 3 | 2 |
| | 55 | 3 | 3 | 1 |
| | 85 | | 1 | |

[a] Reaction performed with 1.19 mmol of 5, 0.54 mmol of 2, and 4 mol % of 1 in 4 mL of refluxing THF. [b] Reaction performed with 1.25 mmol of 5, 2.5 mmol of 2 and 7 mol % of 1 in 5 mL of THF at room temperature. [c] Ratios determined by VPC analysis, utilizing a 15% Carbowax on Chromosorb W column at 165 °C and assuming an identical response factor for all the isomers. Retention times are 8.5, 9.25, and 5 min, respectively.

Scheme I. Synthesis of (±)-Gabaculine




[a] See ref. 19. [b] i. LDA, THF, −78 °C and then $I_2$. ii. DABCO. [c] 2% NaOH, $H_2O$,  . [d] 88% $HCO_2H$, 60 °C.

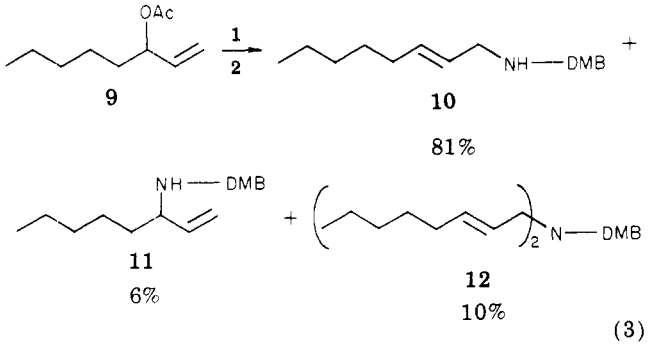
with an excess of the amine 2 and at room temperature. Good yields of dialkylated amine can also be obtained by using the appropriate stoichiometry.

The obtention of a single stereoisomer of 6 was confirmed by $^{13}C$ NMR spectroscopy. Following the reaction by GC reveals that the starting material isomerizes at a rate at least competitive with alkylation as revealed in Table II. Considering the apparently rapid isomerization with substantial buildup of alternative isomers at reflux and yet the emergence of a single aminated product suggests the alkylation is under thermodynamic control which would lead to the assignment of the *E* configuration for the olefin arising from the thermodynamically more stable syn complex.[7] This assignment was verified after removal of the benzhydryl group where a 15-Hz coupling constant could be observed for the vinyl protons.

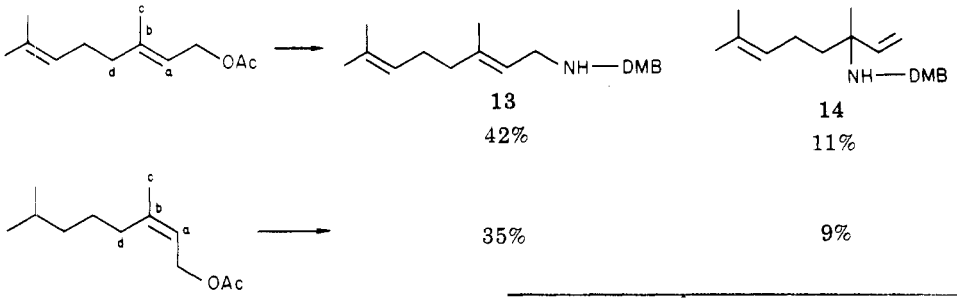
The fact that the various allylic isomers appear to be rapidly equilibrated suggests that a highly stereoselective approach to allylic amines is possible via this method.

(15) B. M. Trost, D. F. Taber, and J. Alper, *Tetrahedron Lett.*, 3857 (1976).

Indeed, starting with the terminal vinyl isomer **9** led to




(3)

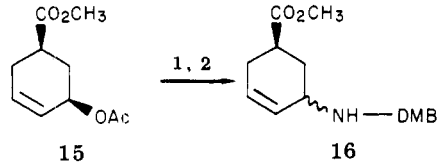



(4)

only the *E* allylic amine **10** in 81% yield in addition to small amounts of two other compounds tentatively assigned as the internal alkylated and dialkylated products—**11** and **12**, respectively (eq 3). The *E* stereochemistry of **10** mainly rests upon the observation of a 15-Hz coupling constant in the corresponding deblocked product (vide infra).

While loss of olefin geometry with disubstituted olefins is rather facile, such stereochemical loss with trisubstituted olefins is much slower. We had previously shown that alkylation of geranyl and neryl acetate with carbon nucleophiles led to complete retention of olefin geometry.[16] In contrast to that observation, both of these allylic acetates gave the same products. The assignment of the *E* configuration for **13** stems from a comparison of the $^{13}C$ NMR spectrum to those of geranyl and neryl acetate (see Table IB). It should be noted that these reactions are appreciably slower than the reactions of allylic acetates of disubstituted olefins. Temperatures around 40 °C are preferred.

Loss of stereochemistry also accompanied the alkylation with the cyclohexenyl acetate **15** (eq 5). The presence of

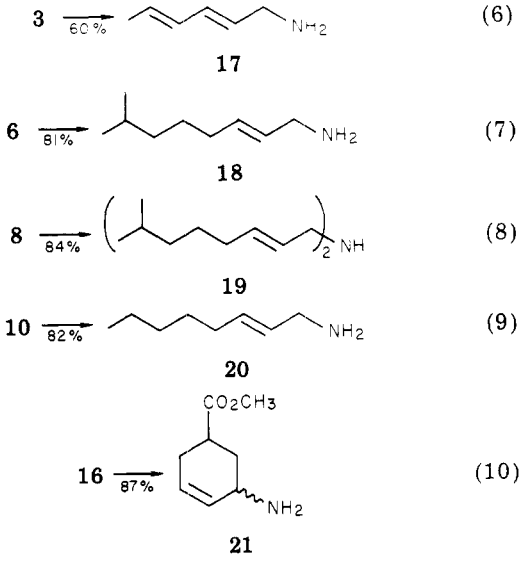



(5)

two isomers in the ratio of 2:3 is clearly indicated by the doubling of absorptions in the proton NMR spectra (see Experimental Section). It is interesting to note that no dialkylation product was observed here too. Following the reaction by VPC showed disappearance of **15** but no appearance of the isomeric *E* isomer of **15**. Other work in these laboratories indicates that such an isomerization can occur with **1**.[17]

(16) B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, **41**, 3215 (1976).
(17) T. R. Verhoeven, Ph.D. Thesis, University of Wisconsin, 1979; B. M. Trost, T. R. Verhoeven, and J. Fortunak, *Tetrahedron Lett.*, 2301 (1979).

With the establishment of the alkylation reaction, we turned our attention to the removal of the substituted benzhydryl group. Use of acetic acid, trifluoroacetic acid, *p*-toluenesulfinic acid, or dry or aqueous hydrochloric acid all gave either recovered starting material or decomposition. On the other hand, 88% formic acid at 80 °C smoothly removes this group. In the workup of this reaction, it is important to remove all excess formic acid by evaporation before adding any water to avoid loss of product. As shown in eq 6–10, both the monoalkylated and dialkylated derivatives are easily converted to the parent amines.




(6) (7) (8) (9) (10)

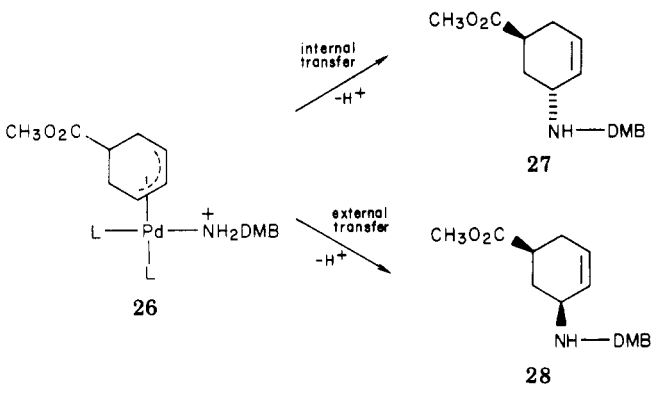
## Synthesis of (±)-Gabaculine

The availability of **21** which is the methyl ester of dihydrogabaculine in 70% overall yield from **15** in a completely regiocontrolled process suggested that a regiocontrolled synthesis of (±)-gabaculine might be in hand.[11,18] This unusual naturally occurring amino acid, first isolated by Mishima and co-workers from *Streptomyces toyocaenis*, is an inhibitor of γ-aminobutyrate aminotransferase, an enzyme that is involved in the metabolism of GABA (γ-aminobutyric acid), an important inhibitory transmitter in the nervous system.

Scheme I outlines the synthesis. The alkylation product **16** was directly subjected to iodination–dehydroiodination as described by Singer and Sharpless[18] to give the protected gabaculine. It is interesting that the dimethoxybenzhydryl group is sufficient to protect the amine during this sequence. The ester was hydrolyzed without complication from elimination with aqueous sodium hydroxide. The solvolytic removal of the DMB group was best monitored by NMR spectroscopy and gave (±)-gabaculine; mp 196–197 °C dec (lit.[11] mp 196–197 °C. The IR, $^1H$

(18) S. P. Singer and K. B. Sharpless, *J. Org. Chem.*, **43**, 1448 (1978).

Scheme II

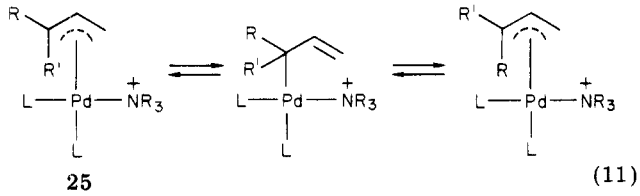



NMR, and $^{13}C$ NMR spectra (the NMR spectra were taken in the presence of disodium acid phosphate as a buffer) were identical with those of an authentic sample. Furthermore, the corresponding hydrochloride had an identical melting point (observed mp 197–199 °C, lit.[11] mp 198–200 °C) with an authentic sample and the mixture melting point showed no depression.

Since **15** is available from 3-cyclohexenecarboxylic acid in 76% yield via a fully regiocontrolled process,[19] (±)-gabaculine is available in yields as high as 45%.

## Discussion

A general stereo- and regiocontrolled approach to primary allylic amines has evolved which uses formolysis for easy removal of a DMB group. The successful synthesis of the sensitive (±)-gabaculine which must simply lose the elements of ammonia to aromatize speaks to the mildness of the deblocking reaction. The complete stereoselectivity for the *E*-olefin isomer regardless of the stereochemistry of the starting allylic acetate indicates rapid olefin isomerization even in the case of trisubstituted olefins. We attribute the difference between carbon nucleophiles and nitrogen nucleophiles in this regard to the formation of $\pi$-allylpalladium–amine complexes like **25**[20] (eq 11) which

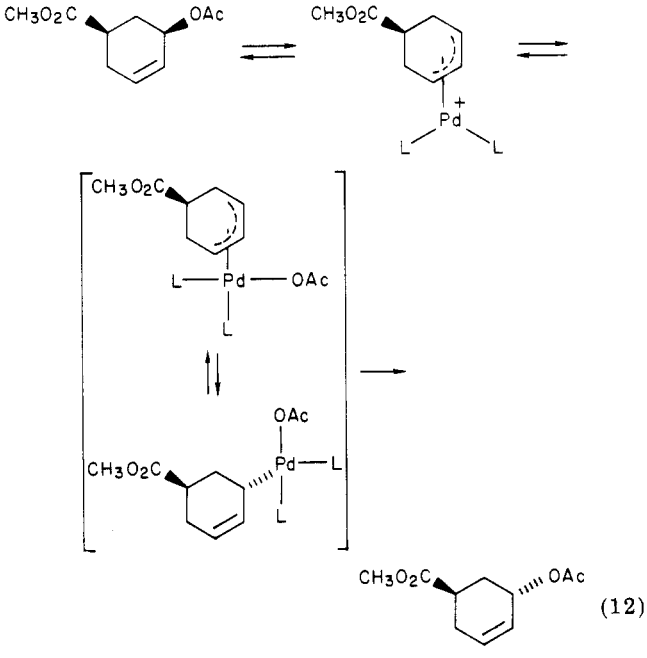



(11)

should facilitate formation of the $\sigma$ complex and thus the olefin isomerization. Addition of basic ligands like pyridine has been known to enhance the syn–anti interconversion.[21] The obtention of the *E* isomers exclusively is more surprising—especially in the trisubstituted cases. Since in trisubstituted olefins the thermodynamic ratio does not so strongly favor the *E* isomer, the high preference must reflect the relative stabilities of the $\pi$-allylpalladium complexes and indicate a much higher stereochemical preference in such systems.

The involvement of complexes like **25** also rationalizes the observed loss of stereospecificity in the reaction with **15**. Thus, the corresponding intermediate **26**[20] can either undergo internal transfer to give **27**, the product of net inversion from the allylic acetate, or normal external displacement of the metal to give **28**, the product of net retention from the allylic acetate (Scheme II).

An alternative possibility for loss of stereochemistry in the overall process is that the starting material epimerizes. Epimerization at the carbon bearing the ester group under such conditions is highly unlikely. Basic epimerization of **16** required use of alkoxide bases in refluxing alcohol or THF, whereas the above reactions only have the amine as a base and can be done at room temperature. Palladium-catalyzed epimerization at the carbon bearing the acetoxy group is an alternative possibility. We have observed this epimerization and have interpreted the results as shown in eq 12.[17] The pathway is, of course,




(12)

analogous to that written for the amine reactions. That this pathway is probably not the cause of the stereochemical loss in formation of **16** stems from the following: (1) the amine reaction proceeds at room temperature, whereas the above required refluxing THF for reasonable rates; (2) following the amine reaction by VPC revealed disappearance of starting acetate but no appearance of the epimer.

We have shown that use of a polymer-bound catalyst can sterically shield the palladium from attack and therefore allow regaining of the stereospecificity of the reaction.[14] Unfortunately, use of DMB-$NH_2$ and **15** with the polymeric catalyst led to such a slow reaction that it was not practical.

In conclusion, use of palladium-catalyzed allylations can provide a convenient entry not only into secondary or tertiary amines but also primary amines. Good yields of either mono- or diallylated amines are possible as a result of the mildness of the alkylating agent. Substitutions on cyclohexenyl systems, which are normally prone to elimination, are highly successful. Because of the success of the amination procedure, a rapid high-yield route to (±)-gabaculine is possible.

## Experimental Section

All reactions were run under a positive nitrogen pressure. THF was distilled from sodium benzophenone ketyl. Silica gel, Macherey Nagel MN-Kieselgel $P/UV_{254}$, was employed for all analytical and preparative TLC. IR spectra were taken on a Perkin-Elmer 267 spectrometer. NMR spectra were taken on

(19) B. M. Trost, J. M. Timko, and J. L. Stanton, *J. Chem. Soc., Chem. Commun.*, 436 (1978); M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, **40**, 1932 (1975).

(20) An equivalent situation would be direct formation of the $\sigma$ complex upon addition of the amine to palladium. We are not attempting to distinguish between these alternatives.

(21) F. A. Cotton, J. W. Faller, and A. Musco, *Inorg. Chem.*, **6**, 179 (1967); D. L. Tibbetts and T. L. Brown, *J. Am. Chem. Soc.*, **92**, 3031 (1970); J. W. Faller, M. E. Thomsen, and M. J. Mattina, *ibid.*, **93**, 2642 (1971); M. Oslinger and J. Powell, *Can. J. Chem.*, **51**, 274 (1973).

Table III. Reaction Details for Allylation Procedure

| acetate, wt (mg), mmol | amt of DMB-$NH_2$ (2), wt (mg), mmol | amt of $(Ph_3P)_4Pd$, wt (mg), mol % | vol of THF, mL | T, °C | time, h | product, wt (mg), % yield | TLC $R_f$ solvent |
|---|---|---|---|---|---|---|---|
| sorbyl acetate | | | | | | | |
| 246, 1.76 | 570, 2.35 | 65, 3% | 5 | reflux | 0.5 | 3, 355, 62%<br>4, 66.6, 19% | 0.35-0.50[a]<br>0.53-0.65 |
| 170, 1.21 | 390, 1.61 | 420, 5%[b] | 4 | reflux | 2.5[c] | 3, 222, 57%<br>4, 32, 13% | as above |
| 174, 1.24[d] | 604, 2.48 | 54, 4% | 5 | RT[g] | 2[e] | 3, 344, 85%<br>4, 41, 16% | as above |
| 5 | | | | | | | |
| 129, 0.70[d] | 204, 0.84 | 30, 4% | 4 | reflux | 0.33 | 6, 164, 64%<br>7, 17, 7%<br>8, 46, 27% | 0.52-0.62[f]<br>0.65-0.72<br>0.72-0.83 |
| 219, 1.19[d] | 133, 0.54 | 60, 4% | 4 | reflux | 2 | 6, 33, 16%<br>7, 14, 7%<br>8, 201, 75% | as above |
| 230, 1.25[d] | 609, 2.50 | 102, 7% | 5 | RT[g] | 1.25 | 6, 366, 80%<br>7, 42, 9%<br>8, 41, 13% | as above |
| 9 | | | | | | | |
| 125, 0.73[d] | 443, 1.82 | 66, 8% | 4 | RT[g] | 1.5[h] | 10, 210, 81%<br>11, 16, 6%<br>12, 17, 10% | 0.26-0.42[a]<br>0.46-0.54<br>0.54-0.63 |
| geranyl acetate | | | | | | | |
| 199, 1.01[d] | 493, 2.03 | 168, 14% | 4 | 40 | 14 | 13, 163, 42% | 0.36-0.51[a] |
| 228, 1.16[d] | 565, 2.32 | 100, 7.5% | 4 | 40 | 21 | 13, 171, 39%<br>14, 51, 11% | as above<br>0.54-0.65 |
| 275, 1.40[d] | 680, 2.80 | 57, 3.5% | 5 | RT,[g] then reflux | 19<br>6 | 13, 212, 40% | as above |
| neryl acetate | | | | | | | |
| 230, 1.17[d] | 570, 2.34 | 99, 7.3% | 4 | 40 | 16.5 | 13, 154, 35%<br>14, 42, 9% | as above[i] |
| 15 | | | | | | | |
| 227, 1.4 | 410, 1.69 | 107, 6.6% | 4 | reflux | 10 | 16, 329, 62% | 0.36-0.47[f] |
| 290, 1.46 | 711, 2.93 | 159, 9.4% | 5 | RT[g] | 1 | 16, 453, 81% | as above |

[a] $C_2H_5OAc$-heptane (1:2). [b] In this case, the polystyrene-palladium(0) catalyst was employed. [c] Following the reaction by VPC revealed conversions of 80% after 30 min, 91% after 60 min, 96% after 90 min, and 100% after 150 min. [d] The allyl acetate was prepurified by collection from VPC (15% Carbowax on a Chromosorb W column at 165 °C for this run). [e] Following the reaction by VPC revealed conversions of 53, 62, 75, and 100% after 15, 30, 45, and 120 min, respectively. [f] $C_2H_5OAc$-heptane (1:1). [g] RT = room temperature. [h] Following the reaction by VPC revealed conversions of 55, 65, 75, 95, and 100% after 10, 20, 35, 60, and 90 min, respectively. [i] For purification, 14 was rechromatographed with 1:3 ether-hexane.

Jeolco MH-100, Brucker 270-MHz, and Jeolco-FX-60 (for $^{13}C$ spectra) spectrometers. Mass spectra were obtained on a MS 902 spectrometer. Melting points are uncorrected. Tetrakis(triphenylphosphine)palladium was prepared by the method of Coulson.[22] 4,4'-Dimethoxybenzhydrylamine was prepared from the corresponding chloride[12,23] by utilizing a procedure adapted from Mandel et al.[24] The chloride was obtained from 4,4'-dimethoxybenzophenone by literature methods.[12,23] The amine was obtained in 73% overall yield from 4,4'-dimethoxybenzophenone after recrystallization by dissolving the crude product in a minimum volume of toluene, placing the flask in a closed chamber over pentane, and allowing the mixture to stand for 24 h at room temperature to give crystalline amine: mp 58–59 °C; NMR ($CDCl_3$) δ 7.32 (d, J = 8 Hz, 4 H), 6.87 (d, J = 8 Hz, 4 H), 5.09 (s, 1 H), 3.68 (s, 6 H), 1.68 (s, 2 H); IR (KBr) 3370, 1610, 1585, 1510 $cm^{-1}$. Anal. Calcd for $C_{15}H_{17}NO_2$: mol wt 243.1259. Found: mol wt 243.1251.

**General Alkylation Procedure.** To a 0.2–0.5 M solution of the allylic acetate in THF was added amine **2** to form a clear solution. Then, 3–8 mol % of the palladium catalyst **1** was added and the solution either stirred at room temperature (preferable) or refluxed with VPC monitoring until the starting allylic acetate disappeared. The reaction mixture was diluted with ether, and the combined organic phase was washed with saturated aqueous sodium bicarbonate. Drying over $MgSO_4$ and evaporation in vacuo gave the crude product which was purified by preparative TLC. In cases where an excess of **2** is employed and one wishes to recover that excess, the ether solution may be washed with cold aqueous 5% hydrochloric acid which selectively extracts the hydrochloride of **2**. The hydrochlorides of the alkylated amines bearing larger alkyl groups remain in the ether layer which is then washed with saturated aqueous bicarbonate as above. In cases where the deblocked amine is desired, the crude material, after the initial bicarbonate wash, may be directly formolyzed and purified at that time. The excess amine **2** is decomposed during formolysis to neutral byproducts which are then easily removed by acid–base workup. The reaction details are summarized in Table III.

**Spectral and Analytical Data. 3**: IR ($CHCl_3$) 3340, 1605, 1585, 1500 $cm^{-1}$; UV $\lambda_{max}$ (ε) 231 (42100), 274 (3400), 284 (2670); NMR ($CDCl_3$) δ 7.23 (d, J = 8 Hz, 4 H), 6.75 (d, J = 8 Hz, 4 H), 5.9–6.2 (m, 2 H), 5.3–5.8 (m, 2 H), 4.73 (s, 1 H), 3.63 (6 H), 3.17 (d, J = 7 Hz, 2 H), 1.73 (s, 1 H), 1.63 (d, J = 6 Hz, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 158.4, 136.5, 131.6, 131.2, 129.3, 128.3, 128.2, 113.8, 65.1, 55.1, 49.4, 17.9. Anal. Calcd for $C_{21}H_{25}NO$: C, 77.99; H, 7.79; N, 4.33; mol wt 323.1885. Found: C, 77.84; H, 7.64; N, 4.15; mol wt 323.1892.

**4**: IR ($CHCl_3$) 1605, 1585, 1503 $cm^{-1}$; UV $\lambda_{max}$ (ε) 230 (77900), 274 (4030), 284 (2600); NMR ($CDCl_3$) δ 7.26 (d, J = 8 Hz, 4 H), 6.80 (d, J = 8 Hz, 4 H), 5.9–6.2 (m, 4 H), 5.3–5.8 (m, 4 H), 4.76 (s, 1 H), 3.73 (s, 6 H), 3.08 (d, J = 7 Hz, 4 H), 1.74 (d, J = 6 Hz, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 158.3, 134.6, 132.8, 131.4, 129.3, 128.3, 127.9, 113.6, 68.2, 55.1, 51.5, 17.9. Anal. Calcd for $C_{27}H_{33}NO_2$: mol wt 403.2511. Found: mol wt 403.2520.

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Table IV. Reaction Details for Formolysis

| benzhydryl deriv, wt (mg), mmol | vol of 88% $HCO_2H$, mL | time, min | product, wt (mg), % yield | TLC[a] $R_f$ | bp, °C ($P$, mm)[b] or mp, °C |
|---|---|---|---|---|---|
| **3**, 413, 1.28 | 2 | 60 | **17**, 75 mg, 60% | 0.38-0.48 | bp 70-80 (75)[c] mp[d] 110-112 |
| **6**, 308, 0.84 | 2 | 30 | **18**, 96, 81% | 0.40 | bp 80-90 (65) |
| **8**, 216, 0.44 | 2 | 40 | **19**, 98, 84% | 0.5-0.8 | bp 100-115 (0.4) |
| **10**, 115, 0.32 | 1.5 | 60 | **20**, 34, 82% | 0.5 | bp 80-90 (65) |
| **16**, 444, 1.16 | 1.5 | 30 | **21**, 157, 87% | 0.39-0.64 | |

[a] Solvent system 80:20:5 $C_2H_5OAc$-$CH_3OH$-$(C_2H_5)_2NH$. [b] Distillation performed on a Kugelrohr apparatus. [c] The initial oily material was distilled at the indicated temperature to give a solid that could be sublimed.[d] [d] Melting point taken in a sealed capillary; could be sublimed at 50-70 °C (60 mm).

**6**: IR ($CHCl_3$) 3340, 1608, 1585, 1500 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.15 (d, $J$ = 8 Hz, 4 H), 6.70 (d, $J$ = 8 Hz, 4 H), 5.43 (m, 2 H), 4.68 (s, 1 H), 3.68 (s, 6 H), 3.06 (m, 2 H), 1.98 (m, 3 H), 1.0–1.5 (m, 5 H), 0.86 (d, $J$ = 7 Hz, 6 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.4, 136.6, 132.6, 128.4, 128.2, 113.7, 65.2, 55.1, 49.8, 38.5, 32.6, 27.9, 27.1, 22.6. Anal. Calcd for $C_{24}H_{33}NO_2$: mol wt 367.2511. Found: mol wt 367.2512.

**7**: IR ($CHCl_3$) 3340, 1608, 1585, 1500 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.10 (d, $J$ = 8 Hz, 4 H), 6.68 (d, $J$ = 8 Hz, 4 H), 5.26–5.54 (m, 1 H), 4.72–5.02 (m, 2 H), 4.70 (s, 1 H), 3.70 (s, 6 H), 2.80 (m, 1 H), 1.68 (s, 1 H), 1.0–1.5 (m, 7 H), 0.82 (d, $J$ = 7 Hz, 6 H).

**8**: IR ($CHCl_3$) 1608, 1585, 1500 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.16 (d, $J$ = 8 Hz, 4 H), 6.67 (d, $J$ = 8 Hz, 4 H), 5.37 (m, 4 H), 4.67 (s, 1 H), 3.63 (s, 6 H), 2.98 (m, 4 H), 1.96 (m, 4 H), 1.0–1.6 (m, 10 H), 0.86 (d, $J$ = 7 Hz, 12 H). Anal. Calcd for $C_{33}H_{49}NO_2$: C, 80.60; H, 10.04; N, 2.85; mol wt 491.3763. Found: C, 80.65; H, 10.02; N, 2.94; mol wt 491.3757.

**10**: IR ($CHCl_3$) 3340, 1610, 1585, 1507 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.14 (d, $J$ = 8 Hz, 4 H), 6.69 (d, $J$ = 8 Hz, 4 H), 5.42 (m, 2 H), 4.67 (s, 1 H), 3.68 (s, 6 H), 3.05 (d, $J$ = 4 Hz, 2 H), 1.97 (m, 2 H), 1.7 (s, 1 H), 1.26 (m, 6 H), 0.87 (t, $J$ = 4 Hz, 3 H). Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96; mol wt 353.2355. Found: C, 78.23; H, 8.91; N, 3.85; mol wt 353.2363.

**11**: IR ($CHCl_3$) 3340, 1610, 1585, 1507 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.12 (d, $J$ = 8 Hz, 4 H), 6.68 (d, $J$ = 8 Hz, 4 H), 5.26–5.62 (m, 1 H), 4.74–5.02 (m, 2 H), 4.70 (s, 1 H), 3.70 (s, 1 H), 2.80 (m, 1 H), 1.45 (s, 1 H), 1.22 (m, 8 H), 0.83 (t, $J$ = 4 Hz, 3 H).

**12**: IR ($CHCl_3$) 1610, 1585, 1507 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.14 (d, $J$ = 8 Hz, 4 H), 6.67 (d, $J$ = 8 Hz, 4 H), 5.34 (m, 4 H), 4.64 (s, 1 H), 3.70 (s, 6 H), 2.94 (m, 4 H), 1.96 (m, 4 H), 1.26 (m, 12 H), 0.87 (t, $J$ = 4 Hz, 6 H).

**13**: IR ($CHCl_3$) 3340, 1607, 1583, 1505 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.12 (d, $J$ = 8 Hz, 4 H), 6.66 (d, $J$ = 8 Hz, 4 H), 5.17 (t, $J$ = 7 Hz, 1 H), 5.0 (m, 1 H), 4.65 (s, 1 H), 3.62 (s, 6 H), 3.07 (d, $J$ = 7 Hz, 2 H), 2.0 (m, 4 H), 1.73 (s, 1 H), 1.63 (s, 3 H), 1.56 (s, 3 H), 1.48 (s, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.5, 137.7, 136.5, 131.2, 128.2, 124.2, 123.0, 113.7, 65.4, 55.0, 45.5, 39.6, 26.6, 25.7, 17.6, 16.2. Anal. Calcd for $C_{25}H_{33}NO_2$: mol wt 379.2511. Found: mol wt 379.2506.

**14**: IR ($CHCl_3$) 3340, 1607, 1583, 1502 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.15 (m, 4 H), 6.68 (m, 4 H), 5.62 (dd, $J$ = 16.5, 12 Hz, 1 H), 4.85–5.07 (m, 3 H), 4.73 (s, 1 H), 3.70 (s, 6 H), 2.0 (m, 2 H), 1.62 (s, 3 H), 1.52 (s, 3 H), 1.5 (m, 2 H), 1.45 (s, 1 H), 0.94 (s, 3 H).

**16**: IR ($CHCl_3$) 3340, 1730, 1607, 1585, 1502 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.28 (d, $J$ = 8 Hz, 4 H), 6.80 (d, $J$ = 8 Hz, 4 H), 5.76 (m, 2 H), 5.01 and 4.93 (s, ratio 2:3, 1 H), 3.76 and 3.75 (s, ratio 2:3, 6 H), 3.67 and 3.66 (s, ratio 3:2, 3 H), 3.18 and 3.13 (m, ratio 2:3, 1 H), 2.74 and 2.52 (m, ratio 3:2, 1 H), 2.23 (m, 2 H), 2.10 (dm, $J$ = 13.4 Hz) and 2.40 (dm, $J$ = 12.5 Hz), for 1 H, 1.53 (s, 1 H), 1.65 (ddd, $J$ = 13.4, 11.8, 4.8 Hz), and 1.41 (td, $J$ = 12.5, 10 Hz) for 1 H. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.45; H, 7.46; N, 3.32.

**Preparation of Amines.** A solution of the benzhydrylamines in 88% formic acid was heated at 80 °C for 20–60 min. Performing the reaction in an NMR tube allowed the following of the reaction by disappearance of the benzhydryl proton. The resulting mixture of a dark red solid suspended in a pink solution was evaporated to dryness in vacuo initially at 15 mm and then at 0.5 mm to ensure removal of all excess formic acid (*important*). The residue was partitioned between ether and water. The ether phase contains the benzhydryl fragment. The water layer was evaporated in vacuo to give the formate salt of the amine. The crude formate was dissolved in chloroform and then a few drops of aqueous concentrated ammonium hydroxide were added. After this mixture was dried over $NaHCO_3$, evaporation at 0 °C gave the free amine which was further purified by TLC and/or distillation. Table IV summarizes the reaction details.

**Spectral and Analytical Data for Amines. 17**: ($CHCl_3$) 3380, 1655 $cm^{-1}$; UV ($CH_3OH$) $\lambda_{max}$ ($\epsilon$) 227 nm (27 300); NMR ($CDCl_3$) $\delta$ 6.0–6.2 (m, 2 H), 5.5–5.8 (m, 2 H), 3.31 (d, $J$ = 6 Hz, 2 H), 1.73 (d, $J$ = 7 Hz, 3 H), 1.28 (s, 2 H). Anal. Calcd for $C_6H_{11}N$: mol wt 97.0891. Found: mol wt 97.0891.

**18**: IR ($CHCl_3$) 3380, 1660 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.54 (m, 2 H), 3.24 (m, 2 H), 2.29 (s, 2 H), 1.98 (m, 2 H), 1.0–1.6 (m, 5 H), 0.86 (d, $J$ = 6 Hz, 6 H); NMR of formate ($CDCl_3$) $\delta$ 5.80 (dt, $J$ = 15, 6 Hz, 1 H), 5.56 (dt, $J$ = 15, 6 Hz, 1 H), 3.42 (d, $J$ = 6 Hz, 2 H), 2.00 (bq, $J$ = 6 Hz, 2 H), 1.0–1.6 (m, 5 H), 0.84 (d, $J$ = 6 Hz, 6 H).

**19**: IR ($CHCl_3$) 3320, 3180, 1665 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.69 (dt, $J$ = 15, 6 Hz, 2 H), 5.39 (dt, $J$ = 15, 6 Hz, 2 H), 3.64 (s, 1 H), 3.33 (d, $J$ = 6 Hz, 4 H), 2.00 (bq, $J$ = 6 Hz, 4 H), 1.1–1.6 (m, 10 H), 0.84 (d, $J$ = 7 Hz, 12 H). Anal. Calcd for $C_{18}H_{35}N$: mol wt 265.2769. Found: mol wt 265.2771.

**20**: IR ($CHCl_3$) 3390, 3460, 1665 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.55 (m, 2 H), 3.24 (m, 2 H), 2.0 (m, 2 H), 1.33 (s, 2 H), 1.28 (m, 6 H), 0.88 (t, $J$ = 6 Hz, 3 H); NMR of formate ($CDCl_3$) $\delta$ 5.90 (dt, $J$ = 15, 6 Hz, 1 H), 5.54 (dt, $J$ = 15, 4.5 Hz, 1 H), 3.53 (bd, $J$ = 6 Hz, 2 H), 2.08 (m, 2 H), 1.32 (m, 6 H), 0.91 (t, $J$ = 6 Hz, 3 H). Anal. Calcd for $C_8H_{17}N$: mol wt 127.1361. Found: mol wt 127.1358.

**21**: IR ($CHCl_3$) 3370, 1725, 1655, $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.7 (m, 2 H), 3.70 (s, 3 H), 3.47 (m, 1 H), 2.5-2.8 (m, 1 H), 2.23 (m, 3 H), 1.95 (s, 2 H), 1.38 (q, $J$ = 12 Hz) and 1.87 (t, $J$ = 4.5 Hz) in ratio of 2:1 for 1 H. Anal. Calcd for $C_8H_{13}NO_2$: mol wt 155.0946. Found: mol wt 155.0945.

**Preparation of (±)-Gabaculine.** To a solution of 5 mmol of lithium isopropylcyclohexylamide in 8 mL of THF and 3.3 mL of hexane (from *n*-butyllithium solution) was added slowly a solution of 363 mg (0.95 mmol) of **16** in 4 mL of THF at −78 °C. After 10 min at −78 °C and 1 h at −63 °C ($CHCl_3$–dry-ice bath), the yellow solution was transferred via a cannula to a −78 °C solution of 1.325 g (5.2 mmol) of iodine in 10 mL of THF with vigorous stirring. Reaction proceeded at −78 °C for 1.5 h, 0 °C for 1 h, and room temperature for 0.5 h. The mixture was diluted with ether, washed three times with aqueous sodium bisulfite and once with saturated aqueous sodium bicarbonate, dried over $MgSO_4$, and evaporated in vacuo at <1 mm. The resulting yellow oil (479 mg) was dissolved in 17 mL of benzene, and 415 mg (3.7 mmol) of DABCO was added. The clear solution was stirred at room temperature for 20 h, diluted with ether, washed with ether–aqueous sodium bicarbonate, dried over $MgSO_4$, and evaporated to dryness in vacuo to give 392 mg of **22** as a crude oil showing one spot on TLC ($C_2H_5OAc$–heptane 1:2): NMR ($CDCl_3$) $\delta$ 7.26 (d, $J$ = 8 Hz, 4 H), 6.98 (d, $J$ = 5 Hz, 1 H), 6.79 (d, $J$ = 8 Hz, 4 H), 6.26 (dd, $J$ = 9, 4 Hz, 1 H), 6.07 (dd, $J$ = 9, 5 Hz, 1 H), 4.97 (s, 1 H), 3.76 (s, 6 H), 3.68 (s, 3 H), 3.36 (m, 1 H), 2.7 (m, 2 H), 1.8 (s, 1 H).

The crude ester **22** was dissolved in 4 mL of 2% aqueous sodium hydroxide and 9 mL of dioxane, and the resulting solution was stirred 16 h at room temperature. The reaction was diluted with 2% aqueous sodium hydroxide and washed with ether. The

aqueous layer was acidified with acetic acid and extensively extracted with chloroform. After evaporation in vacuo, 243 mg (64%) of **23** as a semisolid, homogeneous by TLC on three different solvent systems, was isolated. Further purification by TLC only led to decomposition. A similar experiment beginning with 45 mg of crude ester in 2 mL of dioxane and 1 mL of 2% aqueous sodium hydroxide for 3 h gave 39 mg (90%) of acid **23**: IR ($CHCl_3$) 3640–2500, 1675, 1608, 1502 $cm^{-1}$; UV ($CH_3OH$) $\lambda_{max}$ ($\epsilon$) 236 (17 600), 275 nm (8780); NMR ($CDCl_3$) $\delta$ 7.52 (bs, 2 H), 7.28 (d, $J$ = 8 Hz, 4 H), 6.88 (m, 1 H), 6.73 (d, $J$ = 8 Hz, 4 H), 6.09 (m, 2 H), 5.02 (s, 1 H), 3.68 (s, 6 H), 3.44 (m, 1 H), 2.89 (dd, $J$ = 18, 7 Hz, 1 H), 2.49 (dd, $J$ = 18, 8 Hz, 1 H).

The above acid (130 mg, 0.36 mmol) was dissolved in 2 mL of 88% formic acid in an NMR tube and heated at 50 °C. Conversions of 24, 41, 59, and 62% were observed after 10, 25, 40, and 70 min. The tube was then heated at 60 °C for 30 min (74% completion) at which time the reaction mixture was evaporated to remove the formic acid and then partitioned between water and ether. The water was evaporated to give 84 mg of crude product. The product was dissolved in a minimum volume of distilled water, applied to a 1 × 21 cm ion retardation resin column (AG 11 A8 resin from Bio-Rad Laboratories), and eluted with water. Four fractions, 5, 20, 10, and 10 mL, were collected. The second fraction upon evaporation gave 56 mg of a white solid, mp 180–183 °C, which by UV analysis contained 28.5 mg (78% yield, based on 74% conversion) of (±)-gabaculine. The second and third fractions yielded 15 mg of solid which contained an additional 1.1 mg (2% yield) of (±)-gabaculine for a total yield of 80%. The (±)-gabaculine was recrystallized by dissolving it in a minimum volume of water, adding 1–2 drops of water, and placing the mixture in a closed chamber over acetone. After standing 24 h, the crystals were collected and had a melting point of 188–190 °C. A second recrystallization raised the melting point to 196–197 °C (lit.[11] mp 196–197 °C). IR, UV, and $^1H$ NMR spectra (in the presence of disodium acid phosphate buffer) are identical with those of an authentic sample: $^{13}C$ NMR ($D_2O$ + $Na_2HPO_4$) $\delta$ 176.0, 133.0, 128.8, 128.3, 128.1, 45.4, 29.9. Anal. Calcd for $C_7H_9NO_2$: mol wt 139.0633. Found: mol wt 139.0635. The hydrochloride was prepared by dissolving the (±)-gabaculine in methanol and adding dry HCl. Recrystallization as described for (±)-gabaculine gave material of mp 197–199 °C (lit.[11] mp 198–200 °C). A mixture melting point (mp 198–200 °C) with an authentic sample was undepressed.

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**Supplementary Material Available:** Mass spectral data (2 pages). Ordering information is given on any current masthead page.

# Transition Metal Promoted Alkylations of Unsaturated Alcohols. Alkylation of Alkynols with Organoalanes Promoted by Group 4a Metal–Cyclopentadienyl Compounds

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Studies on the carbometalation of several alkynols, using bis(cyclopentadienyl)- and bis(methylcyclopentadienyl)titanium dichloride–organoalane systems, are reported. Alkynols of three types were examined: (1) $HO(CH_2)_nC{\equiv}CH$, $n$ = 2, 3, 4; (2) $HOCHRCH_2C{\equiv}CH$, R = $CH_3$, $C_2H_5$; and (3) $HOCH_2CH_2C{\equiv}CR$, $R$ = $CH_3$, $C_2H_5$. Additionally, 3-butyn-1-ol was examined with bis(cyclopentadienyl)zirconium dichloride–organoalanes. Finally, the carbometalation of the trimethylsilyl ether of 3-butyn-1-ol was studied with bis(cyclopentadienyl)titanium dichloride–diethylaluminum chloride. All substrates react to produce substituted olefinic alcohols.

There have been recent studies on the regulated carbometalation of alkynols[1] and alkynes,[2] using organoalanes with group 4 transition-metal compounds. Negishi and co-workers[2] have found that acetylenes react with organoalane–bis(cyclopentadienyl)zirconium dichloride reagents to produce alkenylmetals selectively in high yields. The system is characterized as providing "a novel, selective, and operationally simple route to trisubstituted olefins" with starting alkynes of the type $RC{\equiv}CH$. Also, preliminary investigations were reported[2d] for the alkylation of alkynes with a $Al(CH_3)_3$–$(\eta^5\text{-}C_5H_5)_2TiCl_2$ system which was described as one which would often be complementary to the $Al(CH_3)_3$–$(\eta^5\text{-}C_5H_5)_2ZrCl_2$ reagent. Rausch and Boon[3] reported that photolysis of a $(\eta^5\text{-}C_5H_5)_2Ti(CH_3)_2$–diphenylacetylene solution gave the *syn*-methyl-titanated product in 18% yield. Their work represents the "first definite example of the insertion of unsaturated hydro-

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