7440-09-7; sodium, 7440-23-5; ammonia, 7664-41-7; ferric nitrate, 10421-48-4; 11-bromo-1-(1-ethoxyethoxy)undecane, 73010-84-1; 11-bromo-1-undecanol, 1611-56-9; ethyl vinyl ether, 109-92-2; 1-hexyne, 693-02-7; 1-(1-ethoxyethoxy)-12-heptadecyne, 89998-64-1.

Superimposed Lateral Control of Structure and Reactivity Exemplified by Enantiospecific Synthesis of (+)- and (-)-Gabaculine[1]

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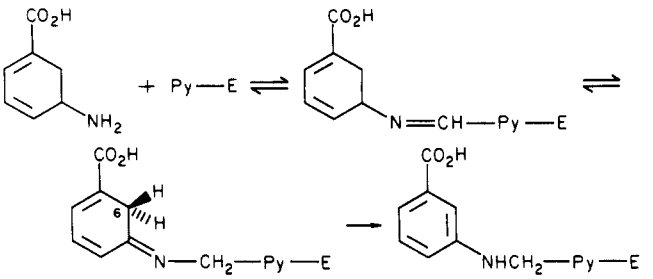
Gabaculine (**6**, R = H), a naturally occurring amino acid,[2] is a potent inhibitor of 4-aminobutyrate:2-oxoglutarate animotransferase (GABA-T), the major GABA catabolizing enzyme. Blocking of this enzyme leads to a buildup of GABA brain levels which may be useful in the treatment of certain diseases characterised by a deficiency of GABA function, e.g., Parkinsonism,[3] epilepsy and, Schizophrenia.[4] The synthesis of analogues for pharmacological examination is therefore desirable. The enzyme-activated mechanism of action of gabaculine has been studied[5] and is shown in Scheme I.

It might be expected that the hydrogen-removal step leading to the enzyme-bound *m*-anthranilic acid derivative would be specific for one of the two C-6 hydrogens. A suitably labeled gabaculine would probably give this information and complete the mechanistic details.

We report the synthesis, using tricarbonyl iron complexes, of gabaculine, in resolved form with known absolute configuration and of enantiospecifically labeled [6-^{2}H]gabaculine as a demonstration of the control features and capabilities of complexes of metal atoms in general and iron in particular.

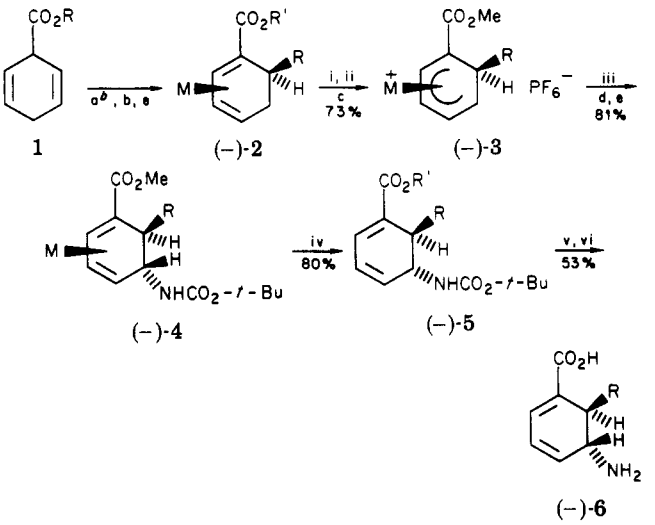
Lateral control as superimposed by π-complexed transition-metal atoms on olefinic bonds leads to new organic synthetic capabilities in bond formations, steric control, and a rational choice of simple precursors.[6,7] It contrasts with classical endogenous control of bond formation and stereochemistry by organic functional groups joined to the skeleton by σ-bonds. These groups in most cases need protection, modification, or removal, and they often do not permit complete steric, including chiral, control. In substituted complexes there is also an element of endogenous control of regiospecificity and reactivity (exemplified by the CO_2Me below in directing the position and rate of nucleophilic attack). However, the organic group is there as a desired structural unit, not primarily to permit formation of the new C–N bond which depends on the cationic nature of the $Fe(CO)_3$. Although the use in synthesis of complexed transition metals is widespread, the present example is one of the few where each major step of a synthetic sequence has been controlled by a different feature of the complexation as shown in Scheme II. Some of the initial steps have been described before but are included here in connection with the role of the complexing group.

Scheme I[a]



[a] Py-E = enzyme-bound pyridoxal phosphate.

Scheme II[a]



[a] Reagents: (i) CH_2N_2, Et_2O; (ii) $Ph_3C^+PF_6^-$, CH_2Cl_2; (iii) H_2NCO_2-*t*-Bu (2.2 equiv), Hunig's base, CH_2Cl_2, 0 °C, 5 min; (iv) Me_3NO, CH_3CONMe_2, −15 °C, 3 h, then 0 °C, 16 h; (v) NaOH, MeOH, H_2O (ref 5, 8, 9); (vi) 3 M HCl, MeOH, ion-exchange column (ref 8). M = $Fe(CO)_3$. [b] The letters a, b, etc., refer to subheadings in the main text.

The lateral control features are as follows.

(a) Catalysis of Formation and Structural Control of the (±) Precursor Comprising 2 (R = R′ = H) [Exemplified by Transformation 1 → 2]. Base-catalyzed conjugation of cyclohexa-2,5-dienoic ester **1** (R = Me) prepared from benzoic acid by Birch reduction,[10] followed by complexation with $Fe(CO)_5$ gives substantially pure 2-carbomethoxycyclohexadiene–$Fe(CO)_3$ complex. The presence of the metal permits acid-catalyzed isomerization entirely into the more stable 1-carbomethoxy complex.[11] The initial isomerization of the uncomplexed ester does not give the 1-CO_2Me derivative, although this is the more stable. With deutero acid the same control in the complex

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leads to the $^2H_1$-isomer **2** (R = ^2H, R′ Me), the deuterium being transferred in an internal process from the metal. Incorporation of a second deuterium, at the 5β-position, is a much slower process in this example.[11] Usefully, if **2** (R = H, R′ = Me) is resolved, deuteration occurs more rapidly than racemization. Such acid-catalyzed reactions, made possible only by virtue of the metal-stabilization of cationic intermediates, were typically carried out in methanolic sulfuric acid during a 24-h reflux period with recoveries of better than 90–95%.

(b) Conversion of an Achiral Precursor into a Chiral Reactant [Exemplified by the Transformation 1 → (+)- and (−)-2 (R = H)]. Any unsymmetrical olefin, itself not chiral, if stably complexed laterally, provides a chiral molecule. Complex **2** (R = H or ^2H, R′ = H) was resolved through the phenylethylammonium salt; formula **2** represents the absolute configuration of the (−)-isomer.[12] The salts are separated by simple crystallization from chloroform or acetone and are easily reconverted into the carboxylic acids by treatment with dilute HCl in ethanol. Methylation and hydride abstraction, which occurs only from the face opposite the metal and only at C-5, gives the resolved cation **3** (R = H or ^2H) with defined absolute configuration. Although in principle the resolution step can be avoided by chiral transfer of $Fe(CO)_3$ from a suitable donor complex,[13] the procedure has not yet been fully developed to allow preparation of new fully resolved complexes with predictable configurations.

(c) Reactivity as a Carbocation [Exemplified by the Transformation 2 → 4]. Cations of type **3** have the charge mostly on Fe[14] but nevertheless react with most nucleophiles as carbocations, at a terminus. This capacity is here superimposed by the $Fe(CO)_3$ and does not require classical organic substituents. However with **3** the CO_2Me directs regiospecificity and increases reaction rate.[15]

(d) Control of Stereochemistry [Exemplified by the Transformation 3 → 4]. Irreversible additions of carbon nucleophiles leads to α-exo addition relative to $Fe(CO)_3$. We have previously noted[16] the beneficial use of diisopropylethylamine to assist addition to cations of heteroatom nucleophiles. Treatment of cation **3** (R = H or ^2H) in CH_2Cl_2 at 0 °C with 2.2 equiv of *tert*-butyl carbamate and 1 equiv of Hunig's base causes dissolution of the salt and formation of the neutral adduct. The reaction may be monitored by using the infrared spectrum, or, more conveniently, by noting complete disappearance of the salt. Extractive workup and chromatography gives pure **4** (R = H or ^2H). Other nitrogen nucleophiles have been used, e.g., phthalimide, sodium amide, ammonia, or hexamethyldisilazane, but were found to be unsatisfactory either at the addition stage or else at the stage of removal of the protecting group.

(e) Enantiospecific Generation of a New Asymmetric Center at Full Resolution and Known Absolute Configuration [Exemplified by the Transformations 1 → (±)-2 (R = H) → 2 (R = D) and 3 → 4]. If the precursor is optically resolved and of known configuration, the complete reaction stereospecificity noted inevitably leads to a new fully resolved center of deducible configuration. The absolute configuration of **4** (R = H) is 5*S* as shown by starting from the known (1*S*)-**2** (R = R′ = H). Other stereospecific reactions include deuteration to **2** (R = ^2H, R′ = H or Me), which, as mentioned, involves addition and loss, of protons or deuterons on the same face as $Fe(CO)_3$.[17] It follows that the new asymmetric center due to ^2H vs. H is fully resolved and of absolute configuration shown in **2** (R = ^2H). Likewise, an asymmetric center due to ^2H vs. H is also produced by borodeuteride reduction of the cation. Removal of metal from (+)-**2** (R = ^2H, R′ = Me) with Me_3NO in the cold gave a deuterated diene ester, $[\alpha]^{25}_D$ 0.65°. The mass spectrum shows a deuterium content, in this sample, of 33%, so the rotation of the pure enantiomer must be about 2°.

Decomplexation of, **4** (R = H) gives the known[2,5] gabaculine precursor **5** (R = H, R′ = Me), contaminated with *m*-anthranilic acid. Without purification the ester was hydrolyzed under conditions which do not convert into acid salt any remaining complexed ester.[18] Standard procedures[5,8] were applied to obtain natural (5*S*)-gabaculine (**6**, R = H) from its N-protected precursor **5** (R = R′ = H).

Completion of the synthesis from a more highly deuterated precursor yielded (−)-gabaculine (**6**, R = ^2H) with a $^2H_1$ content of 75–80%.

The procedure represents one solution to a classical stereochemical problem of producing new asymmetry at full resolution and then removing completely the inducing asymmetry.

The absolute configuration of natural (−)-gabaculine is now defined for the first time by means of a new and more extensively applicable type of procedure. This involves the synthetic induction of a center of known absolute configuration by asymmetry due to the geometry of the superimposed and readily removed metal complexing group. It avoids the necessity to start with a precursor containing a defined center within its skeleton.

The type of process is probably applicable to a broad range of substituted benzoic acids, leading to analogues of the natural inhibitor.

Experimental Section

General experimental details have been given previously.[6] 2,5-Dihydrobenzoic acid was obtained as described.[10] However, for our purpose we did not isolate the pure acid but instead carried out the methylation and isomerization on the crude reaction residue as follows. To an ice-cooled suspension in methanol (ca. 25 mL/g) of the residue obtained after evaporation of ammonia in the Birch reduction of benzoic acid was cautiously added excess dimethyl sulfate (ca. 7 mL/g) and KOH (ca. 2 g/g). The mixture was stirred 30 min at room temperature and then heated at reflux for 5 h. The cooled solution was diluted with water and extracted with light petroleum spirit. The combined extracts were washed with a solution of aqueous ammonia and then water, dried, and evaporated at aspirator pressure to yield the dihydrobenzoic ester.

Complexation with $Fe(CO)_5$ under thermal conditions gave tricarbonyl(2-carbomethoxycyclohexa-1,3-diene)iron.[11,19] This ester was converted to the 1-carboxylic acid by a slight variation to the published procedure.[11] The ester (22 g) and concentrated sulfuric acid (40 mL) in methanol (200 mL) were heated under reflux for 24 h. Some methanol (ca. 100 mL) was removed under reduced pressure (aspirator) from the cooled solution. Water (200 mL) was added and the mixture was heated under reflux for a

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further 30 h. Extractive workup as described gave the 1-carboxy complex (19.8 g, 95%).

Resolution of the 1-CO_2H Complex (2, R = H or ^2H, R′ = H). (−)-1-Phenylethylamine (9.5 mL, 75 mmol) was added dropwise to a stirred solution of the acid (19 g, 72 mmol) in chloroform and acetone (3:1, 400 mL). After 30 min the precipitate was collected and washed with chloroform. The washings and filtrate were set aside. Recrystallization twice from chloroform of the precipitate gave a pure diastereomer (7.4 g), $[\alpha]^{25}_D$ +68° (acetone, *c* 1). The combined washings and filtrate were concentrated and cooled at 0 °C overnight to give a second crop (6.2 g), $[\alpha]^{25}_D$ −95° (acetone, *c* 0.1), which after a further recrystallization from chloroform provided a second pure diastereomer (3.3 g), $[\alpha]^{25}_D$ −126° (acetone, *c* 0.1). Repetition of the above crystallization procedure on combined washings and filtrates provides a further 0.4 g of pure (+)-isomer and 2.6 g of pure (−)-isomer.

The separated diastereomeric phenylethylammonium salts were each dissolved in EtOH containing 2 M HCl (aq). The solution was partitioned between ether and water, the organic phase was separated and washed with 2 M HCl (aq) and water, and then dried and evaporated to give the corresponding acids in quantitative yield. The (−)-salt gave the (−)-acid $[\alpha]^{25}_D$ −136° (*c* 0.1, acetone). Spectral data were as already reported.[11] The absolute configuration of this isomer is as shown in the text and is 1*S*.

((1*S*)-1-Carbomethoxycyclohexadienylium)iron Hexafluorophosphate (3, R = H). An ether solution of the (−)-acid (2.2 g in 20 mL) was treated with diazomethane (0.5 g) in ether (30 mL) at room temperature for 30 min. Formic acid (0.5 mL) was added to destroy any excess CH_2N_2. Evaporation gave the 1*S* ester as a yellow oil which was purified by column chromatography (silica gel, 10% EtOAc in hexane): 2.3 g (100%); $[\alpha]^{25}_D$ −115° (*c* 0.3, $CHCl_3$). Spectral data were as reported for the racemic material.[11]

A solution of this ester (2.2 g) in dry hexane (10 mL) was added dropwise with constant swirling to a solution of trityl hexafluorophosphate (4 g) in dry CH_2Cl_2 (35 mL). Any precipitate forming during the addition was redissolved by using a minimum volume of CH_2Cl_2. After standing 3 h the orange precipitate was collected and washed with reagent-grade ether. The solid was purified by precipitation with ether of an acetone solution to give the pure salt: 2.4 g (73%); $[\alpha]^{25}_D$ −162° (*c* 0.3, acetone). Unreacted starting material (ca. 16%) was recovered.

[(1*S*,5*S*)-1-Carbomethoxy-5-[(*tert*-butoxycarbonyl)amino]cyclohexadiene]iron (4, R = H). To a stirred mixture of the (−)-1-CO_2Me salt (2 g) and *tert*-butyl carbamate (1.21 g) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise diisopropylethylamine (0.86 mL). The resultant clear yellow solution was stirred for 5 min and then diluted with hexane (20 mL). Filtration then solvent removal left an oily solid which was heated in vacuo (50–60 °C, 0.1 torr) to remove excess *tert*-butyl carbamate. Chromatography over silica gel (15% EtOAc in hexane) gave the complex as a yellow oil, 1.5 g (81%). A sample was recrystallized from hexane: mp 116–118 °C; ^1H NMR ($CDCl_3$) 6.2 (d, *J* = 4 Hz, 1 H), 5.4 (t, *J* = 4 Hz, 1 H), 4.3 (m, 2 H), 3.68 (s, 3 H), 3.3 (m, 1 H), 2.82 (dd, *J* = 16, 10 Hz), 1.22 (s, 9 H), 1.1 (br d, *J* = 16 Hz, 1 H); IR ($CHCl_3$) 2065, 2000, 1710 cm^{-1}; MS, *m/e* (relative intensity) 393 (M^+) (2), 365 (5), 337 (16), 309 (39), 253 (45), 193 (82), 134 (89), 105 (100); $[\alpha]^{25}_D$ −52° (*c* 0.2, $CHCl_3$). Anal. Found: C, 48.7; H, 4.8; N, 3.4; Fe, 14.0. Calcd for $C_{16}H_{19}FeNO_7$: C, 48.9; H, 4.9; N, 3.6; Fe, 14.2%.

(5*S*)-5-[(*tert*-Butoxycarbonyl)amino]cyclohexadienecarboxylic Acid (5, R = R′ = H). The complex from above (1 g) was dissolved in dimethylacetamide (10 mL) and the solution was cooled to −10 °C before adding trimethylamine *N*-oxide dihydrate (3 g). The mixture was stirred at this temperature for 3 h and then at 0 °C overnight. The crude diene ester was obtained following filtration (Celite) and extractive workup. ^1H NMR of the product showed the presence of about 10–15% aromatic material. Methanol (5 mL) and 2 M NaOH (2.5 mL) were added to this compound without further purification. After being stirred for 2.5 h, the solution was acidified with 2 M HCl and the acid collected. The acid was obtained as a white solid after recrystallization from ether–hexane: 0.4 g (66%); mp 147–149 °C (lit.[5] 147–148 °C); ^1H NMR ($CDCl_3$) 7.15 (m, 1 H), 6.16 (m, 2 H), 4.55 (br, ca. 2 H, [NH]), 2.68 (dd, *J* = 7, 2 Hz, 2 H), 1.45 (s, 9 H); MS, *m/e* (relative intensity) 237 (M^+ − 2) (5), 183 (20), 137 (28), 122 (35), 57 (100); IR ($CHCl_3$) 1720 cm^{-1}; $[\alpha]^{25}_D$ −249° (*c* 0.1, $CHCl_3$).

(5*S*)-5-Aminocyclohexa-1,3-dienecarboxylic Acid (Natural Gabaculine; 6, R = H). This was prepared from the *t*-BOC derivative above as previously described.[5] The spectral data were exactly as described in the literature: $[\alpha]^{25}_D$ −395° (*c* 0.05, H_2O)[20] [(lit. $[\alpha]$ −454° (*c* 1, H_2O)].

Preparation of Deuterated Compounds. Deuterium was incorporated specifically into the 6β-position of the (±)-1-CO_2Me complex as described.[11] However, in the case of the resolved complex some racemization was observed (ca. 15% at 70% $^2H_1$ incorporation). Fully resolved, deuterium-labeled gabaculine was therefore obtained by performing the optical resolution on the (±)-6β-^2H-acid obtained from the corresponding ester (2, R′ = Me, R = ^2H) by D_2SO_4/D_2O hydrolysis.[11] Deuterium levels at the 6β-position could be raised to about 95% by carrying out the sequence two or more times, but this procedure led to increased (up to 35%) ^2H incorporation at C-5β. Deuterium levels were assessed from ^1H NMR and MS spectra, after allowing for natural abundance contributions. A large isotope effect operates in the deuterium sequence and attempts were made to exclude proton sources. Key differences in the ^1H NMR spectra of the labeled compounds are as follows: **2**, see ref 11; **4**, δ 2.82 reduced and 1.1 now a broad singlet; **5**, δ 2.68 now a broad singlet with reduced integration value; **6**, δ 2.7 now a broad singlet with reduced integration value.

Registry No. **2** (R = R′ = H), 51539-46-9; **2** (R = D, R′ = H), 90149-63-6; (+)-**2** (R = R′ = H) (−)-1-phenylethylamine salt, 90242-12-9; (−)-**2** (R = R′ = H) (−)-1-phenylethylamine salt, 75800-57-6; (−)-**2** (R = R′ = H), 75765-30-9; (+)-**2** (R = R′ = H), 75765-29-6; (−)-**2** (R = H, R′ = Me), 90242-13-0; (−)-**3** (R = H), 90242-15-2; (−)-**4** (R = H), 90149-64-7; (−)-**4** (R = D), 90149-65-8; (−)-**5** (R = R′ = H), 90242-16-3; (−)-**5** (R = D, R′ = H), 90171-27-0; (−)-**6** (R = H), 59556-29-5; (−)-**6** (R = D), 90171-28-1; H_2NCO_2-*t*-Bu, 4248-19-5; tricarbonyl(2-carbomethoxycyclohexa-1,3-diene)iron, 51539-41-4.

(20) Contaminated with 6–7% *m*-anthranilic acid.

2 + 2 Cycloaddition of 4-Substituted-1,2,4-triazoline-3,5-diones to Diphenylketene

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Staudinger reported over 70 years ago that diphenylketene under went 2 + 2 cycloaddition with azobenzene.[1,2] It was found that the reaction with the trans isomer was very slow even at elevated temperature, but the *cis* isomer reacted rapidly at room temperature to give 1,2,4,4-tetraphenyl-1,2-diazetidine-3-one.[3] The reaction has been investigated by a number of other workers[3-7] and it has been postulated that it proceeds by a $_2\pi_s + _2\pi_a$ concerted pathway. The main evidence seems to be the almost total lack of regioselectivity in the addition of unsymmetrically

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