°C with slow heating from 25°C, 105 °C with heating from 95 °C) and air stability of **3** clearly distinguish it from the material purported to have the same structure as **3** isolated by Nesmeyanov et al. (mp 69-71 °C, rapidly oxidized).[5] While the multistep synthesis required for the preparation of **3** (seven steps from $Re_2(CO)_{10}$, 7% overall yield) has so far limited our study of its chemistry, we note here the rather surprising observation that **3** is stable toward $N(C_2H_5)_3$ in C_6D_6.

The results reported here suggest that mechanisms similar to that shown in Scheme III should be considered as possible routes for metal-catalyzed CO reduction. While the metal-formyl complex formed in step 1 is probably thermodynamically unstable relative to metal hydride,[10] reactions proceeding through the formyl intermediate might still occur at reasonable rates. The formyl disproportionation (step 2) and metallo ester hydrolysis (step 3) have been demonstrated here. The hydrogenation of metal alkyls (step 4) and the decarboxylation of metal-carboxy complexes (step 5) are well known. (Obviously, chain extension by CO insertion could precede hydrogen cleavage of the hydroxymethyl metal complex.) Finally, it should be noted that the suggested scheme also includes a variant on the water gas shift reaction.[18] Half of the CO is oxidized to CO_2 via disproportionation of the formyl species, while water supplies half of the hydrogen for reducing the other mole of CO.

Note Added in Proof. The reduction of $C_5H_5Re(NO)(CO)_2{}^+PF_6{}^-$ with $Na^+H_2Al(CH_2CH_3)_2{}^-$ in THF provides a more direct synthesis of $C_5H_5Re(NO)(CO)CH_2OH$, **3**, in 45% isolated yield. Graham has similarly observed that reduction of $C_5H_5Re(NO)(CO)_2{}^+BF_4{}^-$ with 2 equiv of $NaBH_4$ in THF-H_2O gives **3**: W. A. G. Graham and J. R. Sweet, *J. Organomet. Chem.*, in press.

Acknowledgment. Support from the Division of Basic Energy Sciences of the Department of Energy is gratefully acknowledged.

Supplementary Material Available: Experimental details for the synthesis of complexes **2, 3** and **6** (2 pages). Ordering information is given on any current masthead page.

References and Notes

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(4) (a) Collman, J. P.; Winter, S. R. *J. Am. Chem. Soc.* **1973,** *95,* 4089-4090. (b) Winter, S. R.; Cornett, G. W.; Thompson, E. A. *J. Organomet. Chem.* **1977,** *133,* 339-346. (c) Gladysz, J. A.; Tam, W. *J. Am. Chem. Soc.* **1978,** *100,* 2545-2547, and references therein. (d) Collins, T. J.; Roper, W. R. *J. Organomet. Chem.* **1978,** *159,* 73-89.
(5) While the preparation of hydroxymethyl complex **3** has been claimed by Nesmeyanov et al. (Nesmeyanov, A. N.; Krasnoslobodskaya, L. L. *Bull. Acad. Sci. USSR* **1970,** 807-811), we have recently shown[1] that this work is probably in error—a conclusion verified by the present work.
(6) The bistrifluoromethyl derivative of a hydroxymethyl complex, $(C_5H_5)Fe(CO)_2[C(OH)(CF_3)_2]$ has been reported: Blackmore, T.; Bruce, M. I.; Davidson, P. J.; Iqbal, M. Z.; Stone, F. G. A. *J. Chem. Soc. A* **1970,** 3153-3158.
(7) Gladysz, J. A.; Selover, J. C.; Strouse, C. E. *J. Am. Chem. Soc.* **1978,** *100,* 6766-6768.
(8) Experimental details are available as supplementary material.
(9) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill Book Co.: New York, 1968.
(10) Neumann, S. M. Ph.D. Thesis, University of Wisconsin at Madison, 1978.
(11) Removal of solvent from the reaction mixture containg hydroxymethyl complex **3** and methyl ester **5** simply leads to reverse transesterification and the regeneration of dimer **2.**
(12) This unusually rapid ether formation by alcohol condensation is suggested to proceed via the cationic carbene complex $(C_5H_5)Re(CO)(NO)(CH_2)^+$.
(13) Dimer **2** was dissolved in methanol and stirred for 4-5 days and the methanol evaporated. The residue was extracted with heptane (leaving behind methyl ester **5**) and the heptane evaporated to give **6** as an orange oil which gradually solidified to red-orange crystals (85%).
(14) IR (heptane): ν_{CO} 1976, ν_{NO} 1715 (br) cm^{-1}. ^1H NMR (C_6D_6): δ 3.24, s (3 H) 4.80 (s, 5 H), 5.14, 5.30 (AB quartet, J = 9.5 Hz, 2 H).
(15) Other methoxymethyl complexes are known. See, for example, the following. (a) Flood, T. C.; DiSanti, F. J.; Miles, D. L. *Inorg. Chem.* **1976,** *15,* 1910-1918. (b) Green, M. L. H.; Ishaq, M.; Whitely, R. N. *J. Chem. Soc. A.* **1967,** 1508-1515. (c) Jolly, P. W.; Pettit, R. *J. Am. Chem. Soc.* **1966,** *88,* 5044-5045.
(16) IR (THF): ν_{CO} 1961, ν_{NO} 1697 cm^{-1}. ^1H NMR (C_6D_6): δ 4.85 (s, 5 H), 4.87 (s, 5 H), 5.06, 5.16, 5.34, 5.49 (pair of AB quartets, J = 9 Hz, 4 H).
(17) Dimeric ether **7** is also formed when isolated hydroxymethyl complex **3** is treated with catalytic CF_3CO_2H in C_6D_6.
(18) See ref 1 and references therein. For a review see "Catalyst Handbook", Springer-Verlag: London, 1970.

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A New Strategy for Gibberellin Synthesis

Sir:

Although many elegant and ingenious methods have been developed for the preparation of the individual structural features of gibberellic acid (**1**), the total synthesis of the complete molecule has not yet been realized.[1,2] This is presumably due to the lack of a sufficiently efficient and reliable overall strategy. In this paper we describe the preparation of the gibbane derivative **9** by a very efficient sequence, which is sufficiently flexible to be used in the elaboration of **1** itself. The synthesis (Scheme I), which begins with the readily prepared naphthoic acid **2**,[3] is notable for the complete utilization of all the latent functionality contained in the anisole synthon,[6] for the generation of the remaining carbon skeleton from one functional center (C-8), and for its stereoselectivity.

The diazo ketone **3**[7] was the pivotal intermediate in the sequence leading to **9** and was cyclized in trifluoroacetic acid[8] to the dienone **4**, which then underwent an intramolecular Michael reaction to give the tetracyclic diketone **5**.[9] From ^1H NMR spectra it was apparent that one ester methoxyl (δ 3.54) lay in the shielding zone of the 7-carbonyl group,[9a] but that the 15-exo proton (δ 3.24, d, J = 20 Hz) was deshielded by it.[10] These data were consistent only with the diastereomer **5**, and although this stereochemistry differed from the natural gibberellins, it was expected to ensure the development of the correct relative chirality at C-4, C-5, C-9, and C-10.[11,12] Lactonization of the diketo acid, mp 178-180 °C, derived (*n*-PrSLi, HMPA)[13] from **5** was not productive, but the corresponding 7α,16α-dibenzoate, mp 199-200 °C, was converted quantitatively to lactone **6**; the stereochemistry assigned to **6** is expected to be favored both kinetically, and thermodynamically.[11] In preparation for the final stage of the synthesis, **6** was reduced[14] to the C-18 alcohol (*p*-nitrobenzoate, mp 219-220 °C), protected as the methoxymethyl ether,[15] mp 193-194 °C, the C-7 hydroxyl function selectively liberated, and then oxidized to the ketone **7**, mp 169-170 °C. Functionalization of the hindered C-6 position is clearly mandatory for any ring contraction procedure, but all traditional procedures (e.g., acylation, nitrosation, thallation[16]) were completely unsuccessful. The diazo ketone **8** was finally obtained (66% yield) by a novel phase-transfer method,[17] and induced to undergo the photochemical Wolff rearrangement, affording acid **9**, mp 214-215 °C (45% yield, not optimized), as well as a minor amount (10%) of the 6α epimer. Comparison of the ^{13}C NMR spectrum of **9** methyl ester with that of the gibberellin derived **10**[18] and analogous compounds (with allowance for substituent effects) substantiated the assignment of structure **9**.[19] In ^1H NMR spectra H-6 gave rise to a doublet ($J_{5,6}$ = 7 Hz) at δ 2.62 for both **9** and **10**; the 6-epimer of **9** methyl ester showed a doublet ($J_{5,6}$ = 11 Hz) at δ 2.40.[22]

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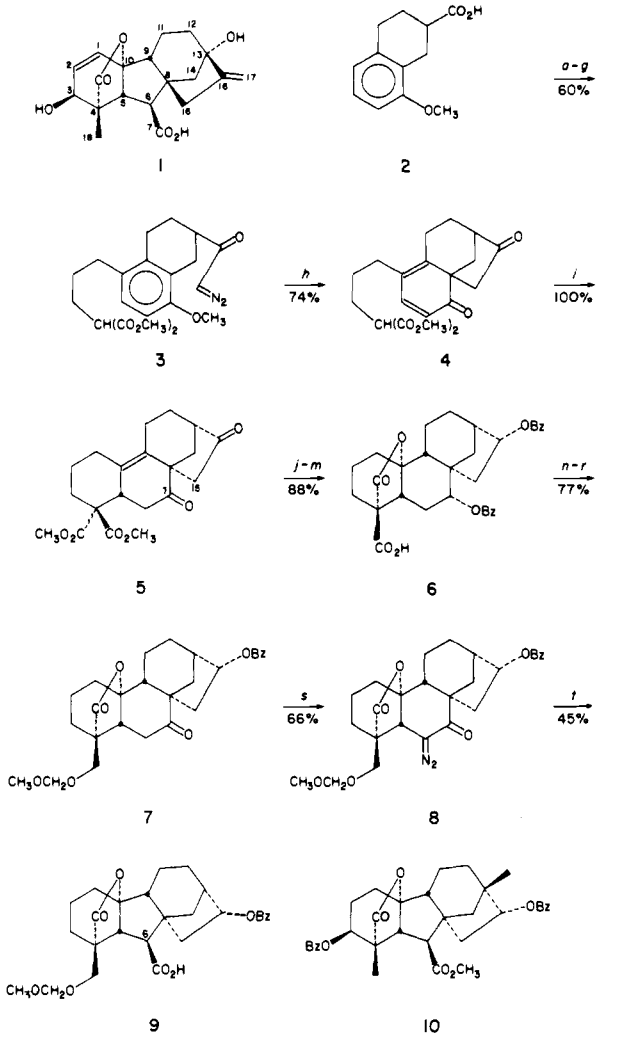
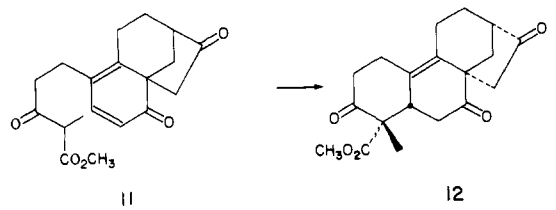
Scheme I



Reagents: [a] $POCl_3$, DMF, 70 °C, 70 h. [b] $PhCH_2Br$, K_2CO_3, DMF, 18 h. [c] CH_2=$CHMgBr$, 0 °C, 1 h; 24 °C, 1 h. [d] $SOCl_2$, CH_2Cl_2, 1 h. [e] $NaCH(CO_2Me)_2$, DMF, 18 h. [f] H_2, PdC (10%), EtOAc. [g] $(COCl)_2$; CH_2N_2, Et_2O, −25 °C, 2 h; 24 °C, 12 h. [h] TFA-CH_2Cl_2 (3:1), −25 °C, 2 min. [i] NaOMe, MeOH, 4 h. [j] $NaBH_4$, EtOH, 0 °C, 1 h. [k] PhCOCl, pyridine, 18 h. [l] *n*-PrSLi, HMPA, 48 h. [m] H_2SO_4-$CHCl_3$ (1:3), 0 °C, 10 min. [n] $ClCO_2Et$, NEt_3, 0 °C, 1.5 h. [o] $NaBH_4$, EtOH, 0 °C, 4 h. [p] $ClCH_2OMe$, $(i\text{-}Pr)_2NEt$, 12 h. [q] K_2CO_3, MeOH, H_2O, 48 h. [r] CrO_3-H_2SO_4-H_2O, Me_2CO. [s] 2,4,6-Triisopropylbenzenesulfonyl azide, 40% KOH, $Bu_4N^+Br^-$, 18-crown-6, PhH, 0.5 h. [t] 450-W Hanovia medium-pressure Hg lamp, pyrex, THF-H_2O, $NaHCO_3$, 5 °C, 0.5 h.

Scheme II



The attainment of the correct gibberellin stereochemistry requires a shift of C-12 from C-13 to C-16.[23] Such a shift would be assisted by the 13-hydroxyl group,[24] which will be required in a synthesis of **1**; current efforts are therefore directed toward incorporating this function.[8] In order to obtain a suitably oxygenated A-ring, the obvious intramolecular Michael reaction of **11** to give **12** was examined (Scheme II). Although the desired relative chirality of C-4 and C-5 was achieved,[25,26] stereochemical control of C-5 relative to C-8 remains elusive. Nevertheless, analogues to **4** and **11** which also possess the pro-13-hydroxyl function are in hand, and we hope to report the total synthesis of gibberellic acid **1** in due course.[27]

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(1) Fujita, E.; Node, M. *Heterocycles*, **1977**, *7*, 709–752; and references cited therein.

(2) Formal total synthesis of the closely related gibberellin GA_4 has been reported,[3] but only through the repeated use of relay intermediates. Only the very simplest C20-gibberellin, GA_{15}, has been prepared in a continuous synthesis.[4]

(3) Mori, K.; Shiozaki, M.; Itaya, N.; Matsui, M.; Sumiki, Y. *Tetrahedron*, **1969**, *25*, 1293–1321.

(4) Nagata, W.; Wakabayashi, T.; Narisada, M.; Hayase, Y.; Kamata, S. *J. Am. Chem. Soc.*, **1971**, *93*, 5740–5758.

(5) Johnson, D. W.; Mander, L. N. *Aust. J. Chem.*, **1974**, *27*, 1277–1286. This acid may also be prepared by *m*etalation (BuLi, TMEDA) at C-7 of 1,6-dimethoxynaphthalene, carboxylation (CO_2), and selective reduction (Li, liq NH_3, *t*-BuOH) of the carboxyl bearing ring.

(6) Recently, emphasis has been placed on the increased efficiency that may be obtained through the use of aromatic synthons and the need for more effective methods for dearomatization: Hendrickson, J. B. *J. Am. Chem. Soc.*, **1977**, *99*, 5439–5450.

(7) Structural formulas, except for **1**, represent racemic compounds. All intermediates were fully characterized by IR, ^1H NMR, and mass spectra and by accurate mass measurements, which were fully consistent with structural assignments. All crystalline compounds gave satisfactory combustion analyses. The numbering system used is in accord with Rowe, J. R., Ed., "The Common and Systematic Nomenclature of Cyclic Diterpenes", 3rd Rev., Forest Product Laboratory, U.S. Department of Agriculture, Wisconsin, 1968.

(8) Blair, I. A.; Ellis, A.; Johnson, D. W.; Mander, L. N. *Aust. J. Chem.*, **1978**, *31*, 405–409, and references cited therein.

(9) Compare with, (a) Burow, K.; Liao, P.; Wheeler, D. M. S. *Syn. Commun.*, **1976**, *6*, 559–561; (b) Isobe, M.; Iio, H., Kawai; T., Goto, T. *Tetrahedron Lett.*, **1977**, 703–706; (c) Stork, G.; Taber, D. F.; Marx, M., *Tetrahedron Lett.*, **1978**, 2445–2448. In these examples the stereochemical outcome is predictable, the reaction geometry favoring the formation of a cis-fused ring. In the present example the factors which influence the chirality of the new asymmetric carbon are quite subtle. It appears that if delocalization of the carbanion is "exocyclic" to the incipient A ring, nucleophilic addition syn to the (future) D ring is preferred. In cases where the delocalization is "endocyclic", e.g., **11**, little selectivity has so far been observed.

(10) A "normal" value for this proton in similar compounds is δ 2.84: Cossey, A. L., unpublished results.

(11) Cf. Barton, D. H. R. *Chem. Ind. (London)*, **1948**, 638; Subluskey, L. A.; Sanderson, T. F. *J. Am. Chem. Soc.*, **1954**, *76*, 3512–3515. These authors derived the trans-transoid-trans stereochemistry for the γ-lactone derived from dihydroisopimaric acid. While later workers[12a] have since derived the cis-transoid-trans configuration, the basic arguments are still valid. In two further pimaric acid lactone derivatives trans-transoid-trans structures were favored.[12b]

(12) (a) ApSimon, J. W.; Holmes, A. M.; Beierbeck; H., Saunders, J. K. *Can. J. Chem.*, **1976**, *54*, 418–422; (b) Ireland, R. E., Mander, L. N. *J. Org. Chem.*, **1967**, *32*, 689–696.

(13) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.*, **1970**, 4459–4462.

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(15) Stork, G; Takahashi, T. *J. Am. Chem. Soc.*, **1977**, *99*, 1275–1276.

(16) McKillop, A.; Hunt, J. D.; Taylor, E. C. *J. Org. Chem.*, **1972**, *37*, 3381–3382.

(17) The method (step s, Scheme I) was developed by Lombardo, L., from a report by Ledon, H. *Synthesis*, **1974**, 347–348; details will be published shortly.

(18) This compound was prepared ($NaBH_4$; PhCOCl, pyridine) from gibberellin *C*-methyl ester (Mulholland, T.P.C. *J. Chem. Soc.*, **1963**, 2606–2616) and had mp 218–219 °C.

(19) The ^{13}C chemical shifts ($CDCl_3$) of C(11)-C(15) in **9** (δ 20.0, 25.8, 39.2, 41.0, 42.6, respectively) agree well with those of the corresponding carbon nuclei of **10** (δ 19.6, 33.8, 44.9, 48.3, 44.4) when correction is made for the substituent effect of the bridgehead 17-methyl group in the latter compound.[20] In contrast, the resonances from C(11)–C(14) (δ 15.3, 19.5, 35.6, 36.1) of the 8β,13β,16β-epimer of 17-nor-**10**[21] all occur at significantly higher field as a consequence of the boat conformation adopted by the cis-fused C-ring.[20] A consistent pattern of similar variations in ^{13}C NMR chemical shifts has been observed in ~40 gibberellin derivatives, although the 7-methoxycarbonyl group causes variable upfield shifts (1–8 ppm) in resonances from either C(14) or C(15), in proportion to their proximity to the ester function: Cossey A. L.; Pyne, S. G., unpublished results.

(20) Stothers, J. B. "Carbon-13 NMR Spectroscopy", Academic Press: New York, 1972; pp 60–69.

(21) Derived ($NaBH_4$; PhCOCl, pyridine) from gibberellin A_4 17-norketone methyl ester: Takahashi, N.; Seta, Y.; Kitamura, H.; Sumiki, Y. *Bull. Agr. Chem. Soc. (Jpn.)*, **1959**, 23, 405–407.

(22) Compare with, Hanson, J. R. *J. Chem. Soc.*, **1965**, 5036–5040.

(23) For examples of the stereochemical inversion of the bicyclo[3.2.1]octane ring system, see Nagata, W.; Narisada, M.; Wakabayashi, T.; Sugasawa, T. *J. Am. Chem. Soc.*, **1967**, *89*, 1499–1504; Mulholland, T. P. C. *J. Chem. Soc.*, **1958**, 2693–2701; Coates, R. M.; Bertram, E. F. *J. Org. Chem.*, **1971**, *36*, 3722–3729, and references cited therein. Bowen, D. H.; Cloke, C.; MacMillan, J. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 378–382.

(24) See, for example, Djerassi, C.; Quitt, P.; Mossetig, E.; Cambie, R. C.; Rutledge, P. S.; Briggs, L. H. *J. Am. Chem. Soc.*, **1961**, *83*, 3720–3722; Mosettig, E.; Beglinger, U.; Dolder, F.; Lichti, H.; Quitt, P.; Waters, J. A. *ibid.*, **1963**, *85*, 2305–2309. For the analogous sulfur assisted rearrangement, see Trost, B. M.; Latimer, L. H. *J. Org. Chem.*, **1978**, *43*, 1031–1040.
(25) Conditions ($PhCH_2N^+(CH_3)_3{}^-OMe/CH_2Cl_2$) favoring the *Z,E*-enolate geometry afforded mainly two tetracyclic compounds (ca. 1:1) with the correct gibberellin C-4, C-5 relative stereochemistry. Conditions ($LiOMe, LiClO_4$, ether) favoring the *Z,Z*-enolate geometry gave two tetracyclic compounds (ca. 1:1) with the opposite C-4, C-5 relative stereochemistry.
(26) Jackman, L. M.; Lange, B. *C., Tetrahedron*, 1977, *33*, 2737–2769, and references cited therein.
(27) NOTE ADDED IN PROOF. The total synthesis of gibberellic acid has been reported since submission of this article: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J-L. *J. Am. Chem. Soc.*, **1979**, *100*, 8035.

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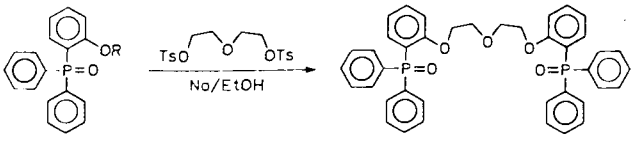
Isolation and X-ray Study of a Host–Guest Complex of an Amino Acid Ester Salt and a Simple Acyclic Ligand Derived from Triphenylphosphine Oxide

Sir:

The design of organic compounds which mimic biologically important phenomena such as molecular complexation is a fascinating challenge.[1] Considerable progress has been made in this area following the introduction of crown ethers[2] and cryptands[3] and a number of complexes of these macrocyclic receptors with ionic and neutral substrates has now been reported.[4] Recently it has been shown that acyclic polydentate ligands can form stable complexes as well.[5]

We describe here the synthesis of a simple acyclic ligand which has the ability to complex ammonium compounds. The complex of an amino acid ester salt and this ligand was isolated and its structure determined by X-ray techniques.

The ligand **2** was prepared as follows. (*o*-Methoxyphenyl)-diphenylphosphine oxide **1a,** mp 175–176 °C, was made in 78% yield from addition of *o*-methoxyphenylmagnesium bromide to diphenylchlorophosphine. Subsequent oxidation of the resulting (*o*-methoxy)diphenylphosphine, mp 126–127 °C, with 30% hydrogen peroxide in acetone[6] and demethylation with hydrogen iodide[7] gave (*o*-hydroxyphenyl)diphenylphosphine oxide **1b,** mp 258–259 °C, in 92% yield. Reaction of 2 equiv of the anion of **1b**[8] with diethylene glycol ditosylate in ethanol at reflux for 3 h afforded the ligand **2** in 94% yield, mp 158–160 °C, after recrystallization from dichloromethane–hexane.[9,10]



1a R = CH_3
1b R = H

2

The affinity of **2** for transition metal ions[11] was demonstrated in a serendipitous manner when in one run we purified **2** by column chromatography. The presence of traces of paramagnetic ions leached from silica gel with **2** in dichloromethane gave rise to broadening of the ^1H NMR spectrum. In addition, **2** formed complexes with ammonium compounds. Cyclohexylamine, isopropylamine, *tert*-butylamine, phenethylamine, and DL-phenylglycine ethyl ester were extracted as ammonium salts from a 0.2 N aqueous perchloric acid solution into chloroform with the aid of **2** at room temperature. After addition of a twofold excess of guest, the 1:1 complexes were found to be present in the organic layer as indicated by ^1H NMR. The selectivity of **2** was remarkable. Methylamine, ethylamine, *n*-propylamine, and *n*-butylamine **1a** were inactive in these extraction experiments. The crucial role of the diethylene glycol moiety was illustrated by preparing a ligand from **1b** and 1,5-dibromopentane (replacement of the central oxygen atom by a methylene function). This ligand obtained in 75% yield, mp 153–154 °C, was totally unable to extract ammonium salts under the conditions described above.

Using the trifluoromethanesulfonate counterion, we successfully isolated the complex of an amino acid ester salt and ligand **2**. When DL-phenylglycine ethyl ester trifluoromethanesulfonate[13] (5 mmol in 3 mL of water) was extracted with **2** (1 mmol in 1.5 mL of deuteriochloroform), the 1:1 adduct was found to be present in the organic layer as indicated by ^1H NMR. Slow addition of diethyl ether caused the complex to crystallize as white needles, mp 159–160 °C. The

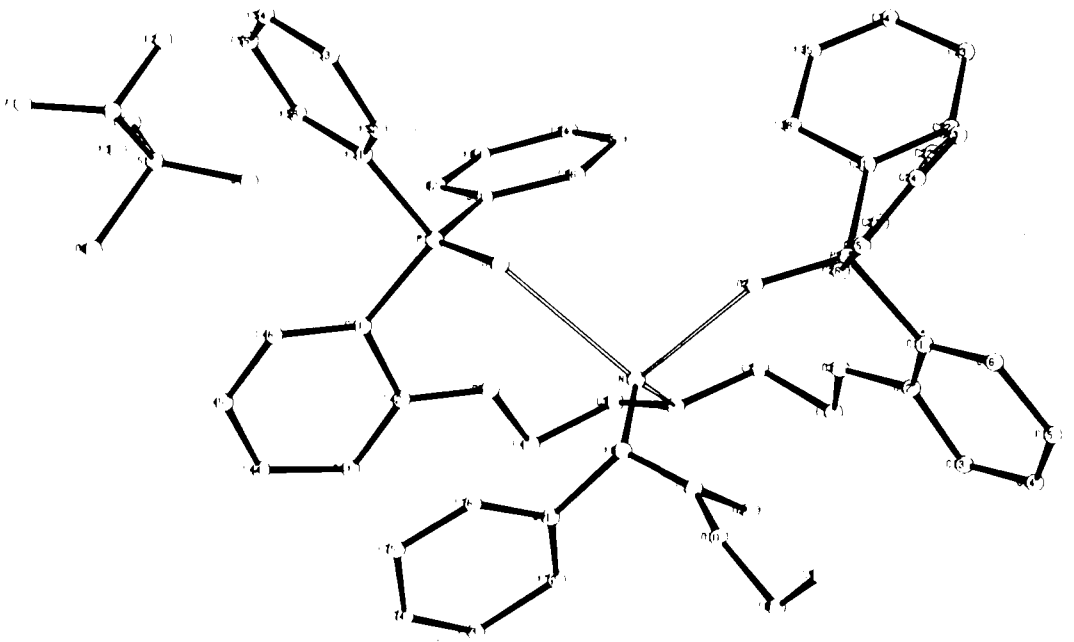


Figure 1. ORTEP drawing of the host–guest complex of **2** with DL-phenylglycine ethyl ester trifluoromethanesulfonate.

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