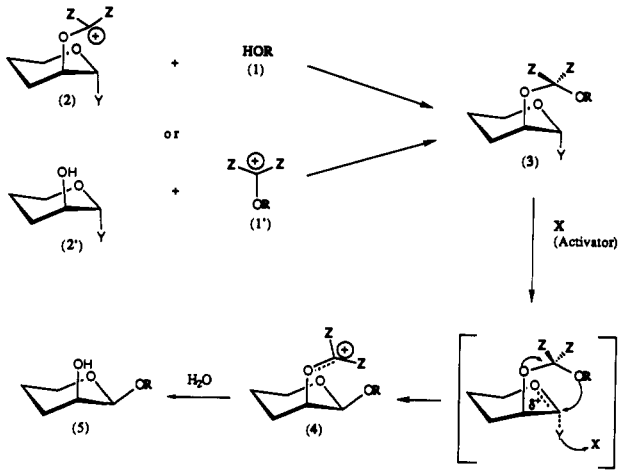
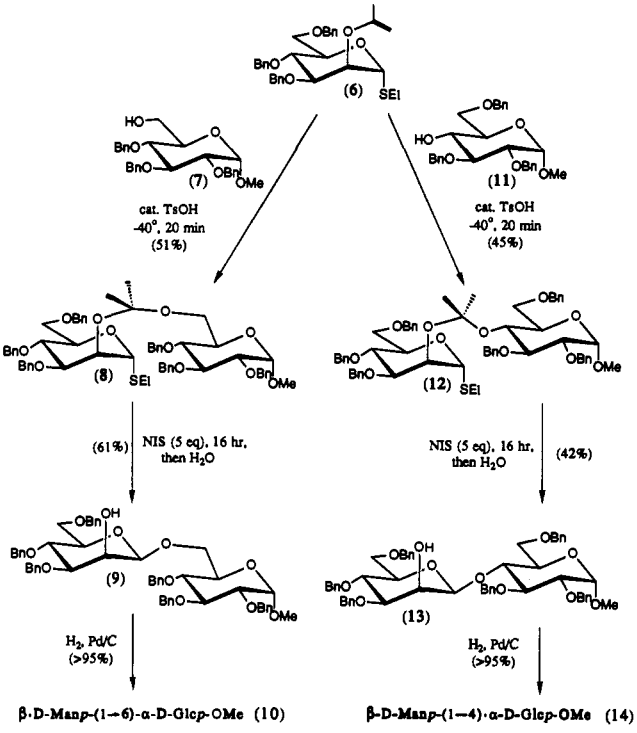
Scheme I



Scheme II



amount of either **7** or **11** produced adduct **8** (51%) or **12** (45%) (Scheme II). No attempt was made to improve these yields since the objective of this work was to evaluate the potential of **8** and **12** to undergo intramolecular rearrangements to β-glycosides. Reaction of **8** or **12** with *N*-iodosuccinimide (NIS, 5 equiv) in dichloromethane was initiated at −5 °C, and the mixture was warmed to room temperature overnight. After aqueous workup and chromatography, the β-linked disaccharide **9** or **13** was obtained in 61% or 42% yield, respectively. The yields were lower when less NIS was used. No α-linked disaccharides could be detected in any of the chromatographic fractions.

We believe that the formation of the β-linked disaccharides occurs intramolecularly for the following reasons. When the rearrangement of **8** to **9** was carried out in the presence of added methanol (1 equiv), the yield of **9** was unchanged. This speaks against a free anomeric carbocation as an intermediate. When the rearrangement of **12** to **13** was performed in the presence of added methanol (1 equiv), the yield of **13** was diminished to 11%, reflecting the well-known lower reactivity of O-4 of glucopyranosides. It is noteworthy that no α-methyl glycoside was formed, only methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (40%), this latter product probably derived by trans-acetalation of **12** with methanol. The methyl aglycon was then delivered intramolecularly as shown in Scheme I (R = CH_3). Compounds **9** and **13** were deprotected to produce disaccharides **10** and **14**.[5]

In conclusion, intramolecular aglycon delivery appears to be a promising new method for the stereospecific synthesis of β-mannosides which can probably also be extended to the formation of other 1,2-*cis*-glycosides. The yields reported have not been optimized, and we expect that a careful study to define groups X, Y, and Z in Scheme I will yield an important new synthetic method for oligosaccharide synthesis.

Acknowledgment. We acknowledge the support of the Alberta Heritage Foundation for Medical Research for a scholarship (F.B.) and the Natural Sciences and Engineering Research Council of Canada.

(5) **10**: ^{1}H NMR (D_2O, 300 MHz) H-1 4.80 (d, J = 3.7 Hz), H-1′ 4.68 (s), H-2′ 4.03 (d, $J_{2',3'}$ = 3.0 Hz), OCH_3 3.41 (s, 3 H); ^{13}C NMR (D_2O, 75 MHz) C-1′ 101.4 ($J_{C1',H1'}$ = 160 Hz), C-1 100.1 ($J_{C1,H1}$ = 170 Hz), OCH_3 56.0. **14**: ^{1}H NMR (D_2O, 300 MHz) H-1 4.80 (d, J = 4.0 Hz), H-1′ 4.74 (s), H-2′ 4.05 (d, $J_{2',3'}$ = 3.0 Hz), OCH_3 3.41 (s, 3 H); ^{13}C NMR (D_2O, 75 MHz), C-1′ 100.8 ($J_{C1',H1'}$ = 160 Hz), C-1 99.9 ($J_{C1,H1}$ = 171 Hz). OCH_3 56.0.

In Situ Complexation Directs the Stereochemistry of N-Glycosylation in the Synthesis of Oxathiolanyl and Dioxolanyl Nucleoside Analogues

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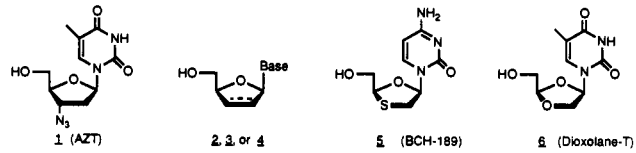
The emergence of 3′-azido-3′-deoxythymidine (AZT, **1**) as an anti-HIV agent has demonstrated the biological importance of nucleosides lacking a 3′-hydroxyl function.[1] Moreover, the discovery that other 2′,3′-dideoxynucleosides inhibit the replication and infectivity of HIV has spurred both the search for superior therapeutic agents and the development of different synthetic approaches to nucleosides.[2] As the result of extensive structure–function studies on nucleoside analogues, a number of 2′,3′-dideoxynucleoside derivatives have been selected for clinical evaluation.[3] These include D4T (2′,3′-didehydro-3′-deoxythymidine, **2**), DDC (2′,3′-dideoxycytidine, **3**), and DDI (2′,3′-dideoxyinosine, **4**).



Recently, the unnatural 3′-heteronucleosides 3′-thia-2′,3′-dideoxycytidine (**5**, BCH-189)[4] and 3′-oxa-3′-deoxythymidine (**6**,

(1) Richman, D. D.; et al. *N. Engl. J. Med.* **1987**, *317*, 192.
(2) Broder, S.; Mitsuya, H.; Yarochoan, R. *Science* **1990**, *249*, 1533.
(3) Mitsuya, H.; Matsukura, M.; Broder, S. In *AIDS: Modern Concepts and Therapeutic Challenges*; Broder, S., Ed.; Marcel Dekker: New York, 1987; p 303.
(4) (a) Belleau, B.; et al. *Abstracts of Papers*, Fifth International Conference on AIDS, Montreal; Abstract No. T.C.O.1, Ottawa, Ontario, 1989. (b) Belleau, B.; Belleau, P.; Nguyen-Ba, N. European Patent Office 90301335.7, 1990. (c) Liotta, D. C.; Choi, W. B. Patent Cooperation Treaty WO 91/11186, 1991.

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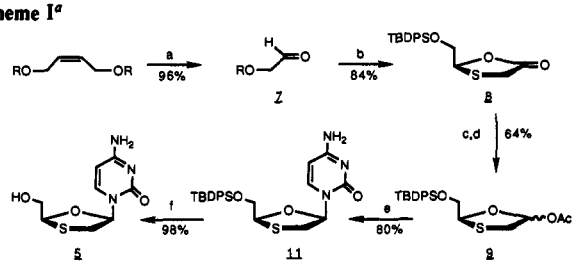
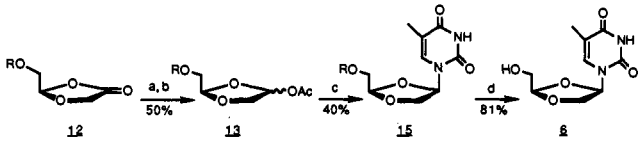
Scheme I[a]



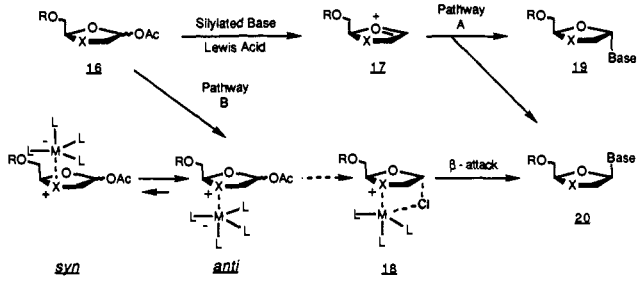
[a] R = *tert*-butyldiphenylsilyl. (a) O_3, Me_2S; (b) $HSCH_2CO_2H$; (c) DIBAL-H; (d) Ac_2O; (e) TMS-cytosine (**10**)/stannic chloride; (f) Bu_4NF.

Scheme II[a]



[a] R = *tert*-butyldiphenylsilyl. (a) $LiAlH(OtBu)_3$; (b) Ac_2O; (c) TMS-thymine (**14**)/dichlorotitanium diisopropoxide; (d) Bu_4NF.

Scheme III[a]



[a] X = S, M = Sn; X = O, M = Ti(Cl); L = Cl or OR.

Dioxolane-T)[5] have been shown to be active against HIV in vitro, but virtually nontoxic to normal cells.[6] These properties suggested the desirability of developing suitable synthetic protocols for preparing a wide array of analogues in these series. Since only the β-isomers generally exhibit useful biological activity, any efficient approaches to these new classes of compounds would likely require a stereoselective nitrogen glycosylation reaction. Here we report general syntheses of both the 3′-thia (**5**) and the 3′-oxa series (**6**) using a highly stereoselective base-coupling reaction which operates via the in situ formation of a complex between a suitable cyclic precursor and an appropriate Lewis acid (see **18**, Scheme III).

In the thia series (**5**), the key intermediate **9** was synthesized from protected glyco aldehyde **7** as shown in Scheme I. Reaction of **7** with mercaptoacetic acid in refluxing toluene produced thia lactone **8** in 84% yield.[7] Reduction of **8** with diisobutylaluminum hydride (DIBAL-H, toluene, −78 °C) or lithium tri-*tert*-butoxyaluminum hydride (THF, 0 °C), followed by trapping of the resulting lactol with acetic anhydride, gave **9** as a 2:1 mixture of anomers in yields of 60–80%. Reaction of this anomeric mixture with silylated cytosine (**10**) and virtually any common Lewis acid resulted in the formation of inseparable mixtures of N-glycosylated anomers.[8] However, use of stannic chloride (2 equiv, CH_2Cl_2) at ambient temperature led to the exclusive formation of the β-cytosine adduct **11**.[9] *This level of selectivity, which we estimate by HPLC to be >300:1, is unprecedented in glycosylation reactions involving the synthesis of 2′-deoxynucleosides and suggests a potentially general approach for controlling the stereochemistry of this important class of reactions.* Our stereochemical assignment was confirmed via an X-ray crystal structure determination on the deprotected nucleoside.[10]

The dioxolanyl compound (**6**) was constructed (Scheme II) in a complementary fashion, except that in this case selectivity was gained through the use of a titanium Lewis acid.[11] As in the thia series, dioxa lactone **12** was produced in 80% yield by the reaction of **7** with glycolic acid in refluxing 1,2-dichloroethane. Reduction with lithium tri-*tert*-butoxyaluminum hydride at 0 °C in THF, followed by reaction with acetic anhydride and 4-(dimethylamino)pyridine, provided the acetyl *O*-glycosides **13** (50% yield, 3.6:1 mixture at the glycosidic center). Reaction of this mixture with dichlorotitanium diisopropoxide and silylated thymine (**14**) in methylene chloride at 25 °C produced the β-dioxolanylthymidine analogue **15** (single isomer by ^1H NMR).[12] Deprotection gave nucleoside **6**, whose physical data were identical with the previously reported physical data for Dioxolane-T (**6**).[13]

The stereoselectivity of these N-glycosylation reactions can be rationalized on the basis of a preferential heteroatom Lewis acid interaction (**18**, Scheme III). Use of Lewis acids (e.g., TMSOTf), whose role is solely to generate an oxonium ion (**17**), should follow pathway A and result in no stereocontrol. However, in cases where the Lewis acid can precomplex to a ring heteroatom (i.e., pathway B), diastereofacial selectivity can be achieved through the minimization of destabilizing 1,2-steric interactions by complexing anti to the protected hydroxymethyl substituent. At the very least, this complexation should dramatically hinder the approach of the silylated base to the α-face. In addition, intermediate **18** could be formed where the associated metal delivers one of its ligands (presumably chloride) to the α-face of the proximal incipient carbonium ion. The resulting α-chloro derivative could then undergo S_N2 attack to form the β-*N*-glycoside.

The case favoring in situ complexation is provided by the following observations: (i) the 3′-heterocycle has no inherent source of facial bias since hydride reduction of the corresponding lactones (**8** and **12**) is relatively nonstereospecific in comparison; (ii) ^{13}C NMR results strongly suggest that stannic chloride selectively complexes with the sulfur atom of both tetrahydrothiophene and 2-substituted 1,3-oxathiolanes; (iii) *the fact that these reactions exhibit a remarkable Lewis acid dependency requires the active participation of the Lewis acid in the reaction transition state*; (iv) these observations also correlate to other results in the literature, i.e., reaction of either acetate **9** or **13** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and silylated bases proceeded with no stereocontrol, analogous to those of 3-substituted 2-deoxyribosides (e.g., N_3, SPh, CN);[14] (v) unlike

(5) Norbeck, D.; Sparton, S.; Broder, S.; Mitsuya, H. *Tetrahedron Lett.* **1989**, 6263.

(6) See refs 4 and 5. In ref 5, the authors report EC_{50} for Dioxolane-T to be 20 μM in ATH8 cells. However, our assay in human peripheral blood mononuclear cells infected with HIV-1 (LAV) indicates that Dioxolane-T has an EC_{50} of 0.09 μM and a therapeutic index greater than 1000. For comparison purposes, BCH-189 has an EC_{50} of 0.01 μM and a therapeutic index greater than 1000 in our assay.

(7) Satsumabayashi, S.; et al. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 913.

(8) For example: (i) with TMSOTf, β:α = 1:1; (ii) with $HgCl_2$, Et_2AlCl, and $TiCl_2(O\text{-}i\text{-}Pr)_2$, no coupling occurs.

(9) Two equivalents of stannic chloride was needed to effect the reaction due to the basicity of the 4-amino substituent on the cytosine ring. This procedure avoids using the *N*-acetyl protected base. We have presented previous evidence in this regard involving 2-arylsulfenyl/$SnCl_4$ controlled N-glycosylations with silylated thymine. See: Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1990**, 1815.

(10) The X-ray crystal structure of **5** has been determined by Dr. Patrick Van Roey of the Medical Foundation of Buffalo. Details of this study will be published separately. In addition to the X-ray structure: (i) the material was identical to an authentic sample provided by Dr. Raymond Schinazi, Emory University; (ii) an NOE experiment on compound **11** showed a 4–7% enhancement at H4′ when H1′ was irradiated.

(11) Unlike stannic chloride, titanium Lewis acids have not found general use in glycosylations. We found that stannic chloride gave a β:α ratio of 1:1 with acetate **13**.

(12) This glycosylation seemed to show a titanium Lewis acid dependent selectivity in both the β:α ratios and the yields (with $TiCl_4$, β:α = 7:1 and 44% yield; with $TiCl_3(O\text{-}i\text{-}Pr)$, β:α = 10:1 and 74% yield). For comparison, reaction of acetate **13** with TMSOTf and silylated thymine (**14**) resulted in a β:α ratio of 1:1 in 73% yield.

(13) This material gave satisfactory analytical and spectral data. An NOE experiment on compound **15** showed a 4% enhancement at H1′ upon irradiation of H4′. The same experiment performed on the α-isomer of **15** showed a 9% enhancement of H6 on the thymidine ring.

the results presented here, stereoselective glycosylations of 2-acylated ribosides which proceed via bridged oxonium ion intermediates exhibit no Lewis acid dependency.

In conclusion, we have presented short, efficient preparations of the oxathiolanyl and dioxolanyl nucleoside analogues, which, as a consequence of their low toxicity, should prove to be important antiretroviral agents. The concept of in situ complexation which we have used here for controlling stereochemistry in the synthesis of these nucleoside analogues should also be applicable to a wide range of other systems and for the preparation of several analogues of **5** and **6**. Further studies involving the preparation and biological activity of these compounds as well as other examples of these types of stereocontrolled glycosylation reactions will be the subject of future reports.

Acknowledgment. This work was supported, in part, by NIH Grant AI-28731. W.B.C. thanks Merck, Sharp and Dohme for a Merck postdoctoral fellowship.

Supplementary Material Available: Physical data including ^1H and ^{13}C NMR, MS, analytical, and IR data for compounds **5**, **6**, **8**, **9**, **11-13**, and **15** (4 pages). Ordering information is given on any current masthead page.

(14) (i) For N_3: $\beta:\alpha$ = 1:1. Chu, C. K.; Beach, J. W.; Ullas, G. V.; Kosugi, Y. *Tetrahedron Lett.* **1988**, 5349. (ii) For CN: $\beta:\alpha$ = 4:5. Okabe, M.; Sun, R.; Tam, S. T.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780. (iii) For SPh: $\beta:\alpha$ = 1:2. Chu, C. K.; Raghavachari, R.; Beach, J. W.; Kosugi, Y.; Ullas, G. V. *Nucleosides Nucleotides* **1989**, *8*, 903.

A Phosphorus Analogue of a Semibridging Aryl Isocyanide Ligand: Synthesis and Structure of (Cl)(PEt$_3$)Pt(μ-C=PR)Pt(PEt$_3$)$_2$(Cl)

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Alkyl and aryl isocyanides (C≡NR) are well-known[1] ligands in transition-metal complexes. They adopt either a terminal (A, Chart I) or bridging (B) mode of coordination to one or two metals, respectively. The phosphorus analogues (C≡PR)[2] of isocyanides are unknown and appear to be unstable[3] relative to the RC≡P isomer.[4] To our knowledge, no complexes containing either terminal (C, Chart I) or bridging (D) C≡PR ligands have been reported. In this paper, we describe the stepwise synthesis of (Cl)(PEt$_3$)Pt(μ-C=PR)Pt(PEt$_3$)$_2$(Cl) (**2**), where R = 2,4,6-tri-*tert*-butylphenyl, and establish that it contains a semibridging C≡PR ligand.

The reaction (eq 1) of Cl_2C=PR[5] (0.359 g, 1.00 mmol) with equimolar Pt(PEt$_3$)$_4$[6] (0.667 g, 1.00 mmol) in 20 mL of benzene at room temperature under nitrogen for 30 min gives the moderately air stable, pale yellow, oxidative-addition product **1**, which is isolated in 85% yield by evaporating the reaction solution to dryness and recrystallizing the residue from hexanes at −78 °C.

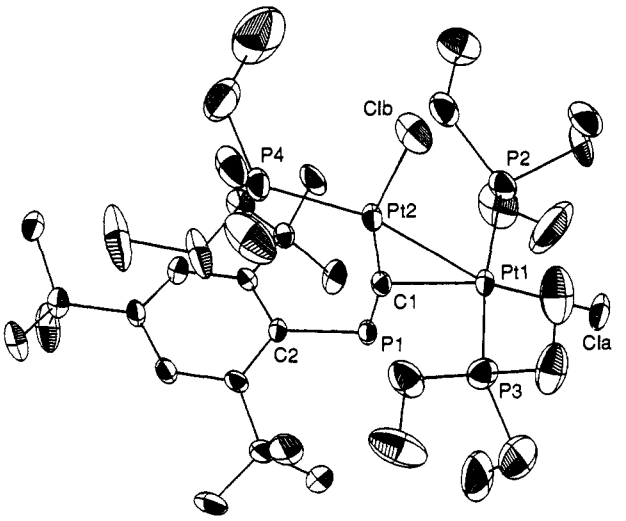


Figure 1. ORTEP drawing of (Cl)(PEt$_3$)Pt(μ-C=PR)Pt(PEt$_3$)$_2$(Cl) (**2**). Selected bond distances (Å) and angles (deg) are Pt(1)-Pt(2) = 2.6751 (5), Pt(1)-C(1) = 2.107 (9), Pt(2)-C(1) = 1.89 (1), P(1)-C(1) = 1.67 (1), P(1)-C(2) = 1.89 (1), C(1)-P(1)-C(2) = 110.7 (5), Pt(1)-C(1)-Pt(2) = 83.8 (4), Pt(1)-C(1)-P(1) = 112.0 (5), and Pt(2)-C(1)-P(1) = 164.1 (6).

Chart I

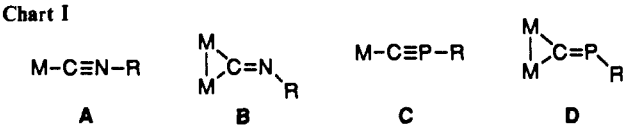
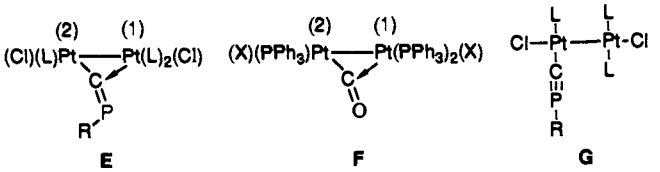
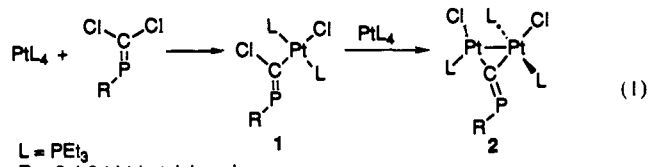


Chart II



Spectroscopic data[7] for **1** are consistent with it having a trans square-planar structure.



(1)

When **1** (0.079 g, 0.10 mmol) is reacted (eq 1) with equimolar Pt(PEt$_3$)$_4$ (0.066 g, 0.10 mmol) in 5 mL of hexanes at room temperature under nitrogen for 2 h, red crystals of **2** are isolated[8] in 65% yield by reducing the volume of the reaction solution and cooling it to −30 °C.

An X-ray diffraction study[9] shows **2** (Figure 1) to be a dinuclear

† Iowa State University Molecular Structure Laboratory.

(1) Singleton, E.; Oosthuizen, H. E. *Adv. Organomet. Chem.* **1983**, *22*, 209.

(2) The recommended Chemical Abstracts name for C≡PR, where R is an aryl group, is (arylphosphinidene)methylene.

(3) Yoshifuji, M.; Niitsu, T.; Inamoto, N. *Chem. Lett.* **1988**, 1733.

(4) Regitz, M. *Chem. Rev.* **1990**, *90*, 191.

(5) Appel, R.; Casser, C.; Immenkeppel, M. *Tetrahedron Lett.* **1985**, *26*, 3551.

(6) Yoshida, T.; Matsuda, T.; Otsuka, S. *Inorg. Synth.* **1979**, *19*, 110.

(7) **1**: ^1H NMR (C_6D_6) δ 7.58 (s, 2 H, R), 1.95 (m, 12 H, CH_2 of Et), 1.71 (s, 18 H, CH_3 of R), 1.35 (s, 9 H, CH_3 of R), 1.03 (m, 18 H, CH_3 of Et); $^{31}P\{^1H\}$ NMR (C_6D_6, 85% H_3PO_4 external standard) δ 223.3 (t, $^3J_{PP}$ = 25 Hz, $^2J_{PtP}$ = 658 Hz from ^{195}Pt satellites, C=PR), 15.0 (d, $^3J_{PP}$ = 25 Hz, $^1J_{PtP}$ = 2753 Hz, PEt_3); EIMS (70 eV) *m/e* 790 (M^+), 755 (M^+ − Cl), 733 (M^+ − *t*-Bu), 698 (M^+ − (Cl + *t*-Bu)).

(8) **2**: ^1H NMR (C_6D_6) δ 7.46 (s, 2 H, R), 2.43 (m, 6 H, CH_2), 2.09 (m, 6 H, CH_2), 1.49 (6 H, CH_2), 1.74 (s, 18 H, CH_3 of R), 1.35 (s, 9 H, CH_3 of R), 1.26 (m, 18 H, CH_3 of Et), 0.82 (m, 9 H, CH_3 of Et); $^{31}P\{^1H\}$ NMR (acetone-d_6, 85% H_3PO_4 external standard) δ 151.3 (d, t, $^3J_{P1P2}$ = 23 Hz, $^3J_{P1P4}$ = 35 Hz, $^2J_{Pt,P1}$ = 321 Hz, $^2J_{Pt,P1}$ = 100 Hz), 22.8 (d, $^3J_{P4P1}$ = 35 Hz, $^1J_{Pt2P4}$ = 4814 Hz, $^2J_{Pt1P4}$ = 512 Hz), 19.6 (d, $^3J_{P2P1}$ = 23 Hz, $^1J_{Pt1P2}$ = 2428 Hz, $^2J_{Pt2P2}$ = 45 Hz). Anal. Calcd for $C_{37}H_{74}Cl_2P_4Pt_2$: C, 40.25; H, 6.78. Found: C, 40.36; H, 6.95.

0002-7863/91/1513-9379$02.50/0