Synthesis of the Carbohydrate Moiety of Bleomycin. 2,3,4,6-Tetra-O-Substituted D-Mannose Derivatives

Alan Millar, Ki Hyup Kim, David K. Minster, Tadaaki Ohgi, and Sidney M. Hecht*†

Departments of Chemistry and Biology, University of Virginia, Charlottesville, Virginia 22901, and Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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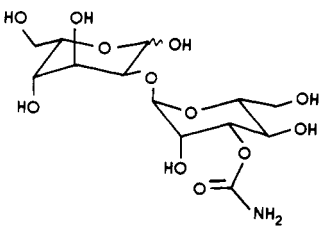
As part of the synthesis of the carbohydrate moiety of bleomycin [2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose], two different approaches were employed for the synthesis of appropriate 3-*O*-carbamoylmannose precursors. One approach, which required introduction of the carbamoyl group following coupling of the L-gulose and D-mannose moieties, involved the preparation of the strained tricyclic ortho ester 4-*O*-benzyl-1,2,3-*O*-orthoacetyl-6-*O*-trityl-β-D-mannoyranose (**6b**). The preparation of this compound and a study of its chemistry is reported. An alternate approach, which provided mannose derivatives of utility for the synthesis of bleomycin, involved the preparation of four compounds that contained the 3-*O*-carbamoyl group prior to condensation with L-gulose. These key intermediates were 2,4,6-tri-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranosyl bromide (**20**), 4,6-di-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**21**), 4,6-di-*O*-acetyl-3-*O*-carbamoyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**22**), and 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannoyranosyl chloride (**23**).

Ongoing synthetic studies of bleomycin group antibiotics[1] required the synthesis of the carbohydrate moiety of bleomycin, 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulose (**1**).[2] Described herein are the preparation of mannose derivatives of potential utility as synthetic intermediates for bleomycin group antibiotics and a practical route to 3-*O*-carbamoyl-D-mannose derivatives blocked suitably for subsequent regio- and stereoselective coupling to the L-gulose moiety of bleomycin.



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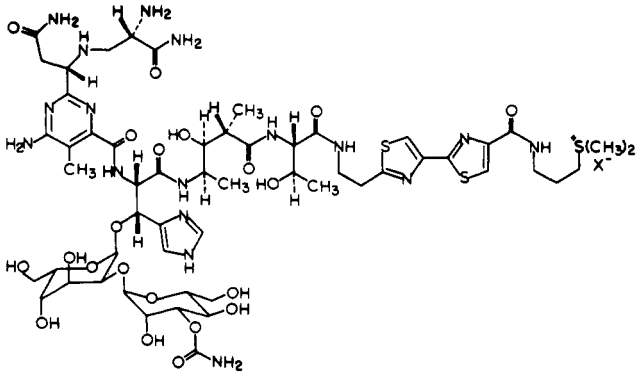
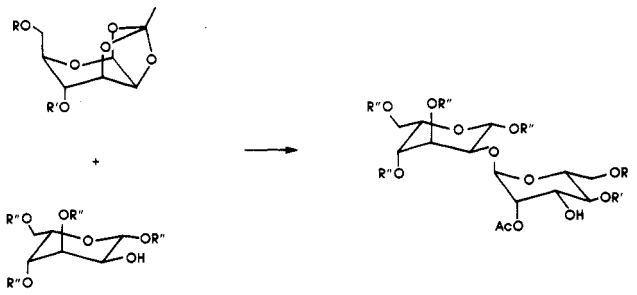


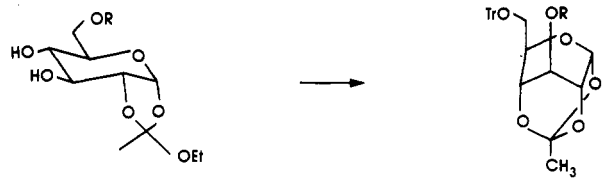
bleomycin A_2

The approach employed initially was based on an earlier observation[2a,3] that attempted tritylation of orthoacetate derivative **2a** provided a low yield of 1,2,4-*O*-ortho-

Scheme I. Proposed Approach for Synthesis of the Disaccharide Moiety of Bleomycin



acetyl-6-*O*-trityl-α-D-glucopyranose (**3a**),[4] in addition to the expected product **2b**. Treatment of **2b** with lutidinium



2a, R = H
2b, R = Tr

3a, R = H
3b, R = Ac

hydrobromide in dichloromethane in presence of 4-Å molecular sieves gave **3a** in 65% yield; the analogous formation of internal ortho esters[5] of D-glucose,[6,7] D-arabinose,[6b] D-xylose,[6b] and L-rhamnose[7] suggested the

† University of Virginia and Smith Kline & French Laboratories. To whom correspondence should be addressed at the Department of Chemistry, University of Virginia.

(1) Aoyagai, Y; Katano, K.; Suguna, H.; Primeau, J.; Chang, L.-H.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5537.
(2) (a) Minster, D. K.; Hecht, S. M. *J. Org. Chem.* **1978**, *43*, 3987. (b) Pozsgay, V.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 3761.
(3) Katano, K.; Chang, P.-I.; Millar, A.; Pozsgay, V.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1985**, *50*, 5807.
(4) Bochkov, A. F.; Zaikov, G. E. "Chemistry of the *O*-Glycosidic Bond: Formation and Cleavage"; Pergamon Press: Oxford, 1979.
(5) Kochetkov, N. K.; Bochkov, A. F. "Recent Developments in the Chemistry of Natural Carbon Compounds"; Akademia Kiadó: Budapest, 1971; Vol. 4.
(6) (a) Bochkov, A. F.; Voznyi, Ya. V.; Kalinevich, V. M.; Shashkov, A. S.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 415; *Chem. Abstr.* **1975**, *83*, 28649x. (b) Bochkov, A. F.; Voznyi, Ya. V.; Chernetsky, V. N.; Dashunin, V. M.; Rodionov, A. V. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1975**, 420; *Chem. Abstr.* **1975**, *83*, 28479a.
(7) Although we are unaware of the preparation of any other 1,2,3-*O*-orthoacetyl-β-D-mannopyranose derivative, the formation of at least one analogous rhamnose derivative in low yield was suggested by ^{1}H NMR analysis of a crude reaction mixture. See: Backinowsky, L. V.; Bryamova, N. E.; Tsvetkov, Y. E.; Betaneli, V. I. *Carbohydr. Res.* **1981**, *98*, 181.

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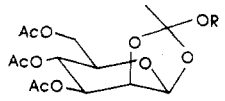
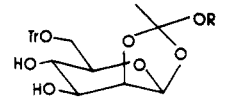
Table I. 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-alkoxyethylidene)-β-D-mannopyranoses 4[9]



compd	R	yield,[a] %	crystal form (mp,[b] °C)	^{1}H NMR,[c] δ
4a	$C(CH_3)_3$	16	colorless needles (110–112)	1.32 (s, 9), 1.81 (s, 3), 2.04 (s, 6), 2.08 (s, 3), 3.90 (m, 1), 4.20 (m, 2), 4.63 (m, 1), 5.35 (m, 3)
4b	$CH(CH_3)_2$	66	colorless needles (85–87)	1.18 (d, 6), 1.66 (s, 3), 2.10 (s, 6), 2.13 (s, 3), 3.80 (m, 2), 4.20 (m, 2), 4.62 (m, 1), 5.24 (m, 2), 5.44 (d, 1, J = 2.5 Hz)
4c	CH_2CH_3	70	white powder (102–103)	1.17 (t, 3), 1.75 (s, 3), 2.05 (s, 3), 2.08 (s, 3), 2.12 (s, 3), 3.50 (m, 1), 3.56 (q, 2), 4.21 (m, 2), 4.60 (m, 1), 5.20 (m, 2), 5.47 (d, 1, J = 2.0 Hz)

[a] From D-mannose. [b] Uncorrected. [c] $CDCl_3$.

Table II. 1,2-*O*-(1-Alkoxyethylidene)-6-*O*-trityl-β-D-mannopyranoses 5



compd	R	yield, %	crystal form (mp,[a] °C)	^{1}H NMR[b] δ	IR,[c] cm^{-1}
5a	$C(CH_3)_3$	42	*d,e*	1.33 (s, 9), 1.77 (s, 3), 2.90 (br s, 2, exchangeable with D_2O), 3.18–4.20 (m, 5), 4.47 (br t, 1, J = 2.5 Hz), 5.30 (d, 1, J = 2.5 Hz), 7.10–7.65 (m, 15)	3440, 1590, 1490, 1450, 1380, 1365, 1240, 1155, 1080, 895, 700
5b	$CH(CH_3)_2$	55	*d*	1.21 (d, 6), 1.76 (s, 3), 3.15 (br s, 2, exchangeable with D_2O), 3.25–4.22 (m, 6), 4.48 (t, 1, J = 2.5 Hz), 5.41 (d, 1, J = 2.5 Hz), 7.05–7.65 (m, 15)	
5c	CH_2CH_3	86	colorless prisms[e] (96–97)	1.17 (t, 3), 1.75 (s, 3), 2.74 (br s, 2, exchangeable with D_2O), 3.10–4.10 (m, 7), 4.43 (t, 1, J = 2.5 Hz), 5.38 (d, 1 J = 2.5 Hz), 7.02–7.60 (m, 15)	3580, 3400, 1570, 1480, 1450, 1205, 1050, 900, 705

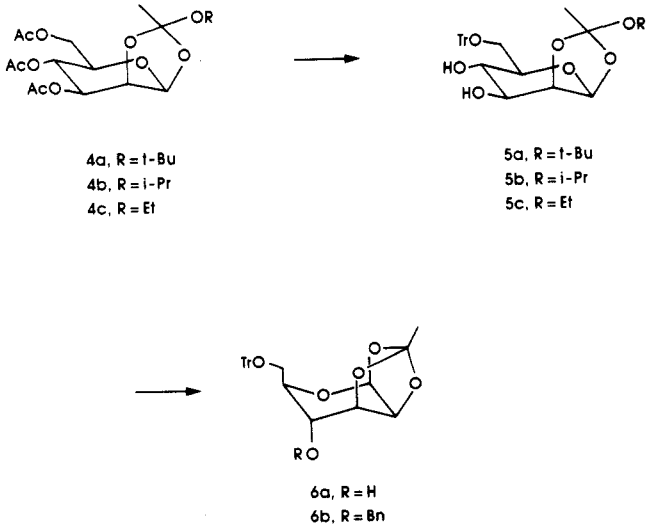
[a] Uncorrected. [b] $CDCl_3$. [c] CCl_4. [d] Foam. [e] Satisfactory elemental analysis obtained.

possible utility of a D-mannose ortho ester for the elaboration of the carbohydrate moiety of bleomycin.

Like their bicyclic analogues, tricyclic ortho esters are glycosylating reagents;[4] however, the formed glycosides contain a free OH group. While the position of this OH group cannot always be specified in advance,[4] use of a 1,2,3-*O*-orthoacetyl-β-D-mannopyranose derivative[7] (e.g., **6b**) might yield directly a disaccharide with the requisite 1,2-trans-glycosidic bond, blocked at C-2 so that a 3-*O*-carbamoyl group could be introduced to give the desired disaccharide derivative directly (Scheme I). Possible difficulties included uncertainty in the position of the OH group in the product[4] and competition for **6b** by the 2-OH group of gulose and the OH group in the formed disaccharide. Indeed, concentrated solutions of **3a** were found to polymerize readily.

However, the 2-*O*-acetate **3b** of the tricyclic ortho ester **3a** was stable in solution. ^{1}H NMR decoupling studies permitted assignment of all resonances; the coupling constants were consistent with those expected for the rigid tricyclic structure.[8] Interestingly, the 3-*O*-acetyl methyl group resonated far upfield (δ 1.70), presumably due to the close proximity of this methyl group to a phenyl of the trityl group.

At the outset of this work there was no literature report of any tricyclic ortho ester of mannose.[7] The novel conversion of a 1,2-*O*-alkoxyethylidene derivative of mannose to the tricyclic ortho ester involving 3-OH appeared likely only if the 6-position were blocked.[7] Accordingly, 1,2-*O*-(1-alkoxyethylidene)-6-*O*-trityl-β-D-mannopyranose derivatives **5** were chosen as potential precursors to tricyclic ortho esters **6**. The greater size and basicity of the alkoxy group in **5a** would presumably facilitate intramolecular trans-ortho-esterification (via an acetonium ion). Ortho esters **4**[9] were prepared from acetobromomannose by the by the methods of Lemieux[10] or Hanessian[11] (Table I). However, while the isopropyl and ethyl orthoacetates **4b** and **4c** were accessible in 66% and 70% yields, respectively, the *tert*-butyl orthoacetate **4a** could be obtained only in 16% yield. The successful preparation of mannose ortho esters in other laboratories,[9,12] as well as the results obtained here with **4b** and **4c**, suggests that the low yield of **4a** reflects rate-limiting capture of the acetoxonium ion by the bulky *tert*-butyl alcohol molecule.



4a, R = t-Bu
4b, R = i-Pr
4c, R = Et

5a, R = t-Bu
5b, R = i-Pr
5c, R = Et

6a, R = H
6b, R = Bn

Triacetates **4** were transformed into the respective 6-*O*-trityl derivatives **5** in reasonable yields (Table II) by deacetylation ($NaOCH_3$, CH_3OH) and tritylation.

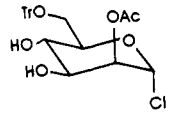
(8) Bochkov, A. F.; Dashunin, V. M.; Kessenikh, A. V.; Kochetkov, N. K.; Naumov, A. D.; Obruchnikov, I. V. *Carbohydr. Res.* **1971**, *16*, 497.

(9) Chapleur, Y.; Castro, B.; Gross, B. *Tetrahedron* **1977**, *33*, 1615.
(10) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2199.
(11) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1975**, *44*, C14.
(12) Perlin, A. S.; Mazurek, M. *Can. J. Chem.* **1965**, *43*, 1918.

Treatment of **5a** with lutidinium hydrobromide in dichloromethane afforded **6a** in 57% yield. However, analogous treatment of the isopropyl and ethyl orthoesters **5b** and **5c** gave **6a** in yields of only 21% and 19%, respectively. The similarity of yields from the ethyl and isopropyl derivatives of **5** thus paralleled the reported[10] similarity in the stability of such ortho esters.

A number of experiments were carried out in an attempt to improve the overall yield of **6a**, including an effort to improve the availability of **5a**, e.g., by transesterification with *tert*-butyl alcohol in the presence of various catalysts. These attempts were unsuccessful, as were efforts to improve the conversion of **5c** → **6a** by variations in concentrations of reactants, reaction temperature, and catalyst.

The reported[13] opening of an ortho ester with stoichiometric amounts of trityl chloride to provide an acetyl chlorohydrin via an intermediate acetoxonium ion suggested the possibility of employing trityl chloride to effect the conversion **5c** → **6a** at low concentrations of Cl^-. Initially, treatment of **5c** with a catalytic amount of trityl chloride in the presence of 4-Å molecular sieves (12 days, 25 °C) gave **6a** in only 14% yield. When carried out in dichloromethane at reflux, the same reaction gave **6a** in 43% yield within 2 days. It was found that the use of trityl chloride in catalytic amounts was essential for obtaining **6a**. As anticipated by the work of Newman and Chen,[13] the use of stoichiometric trityl chloride afforded only glycosyl chloride **7**. Protection of 4-OH in **6a** was accomplished in 94% yield (NaH, $C_6H_5CH_2Br$, 25 °C, 24 h) providing a derivative (**6b**) suitable for use in glycosylation studies.



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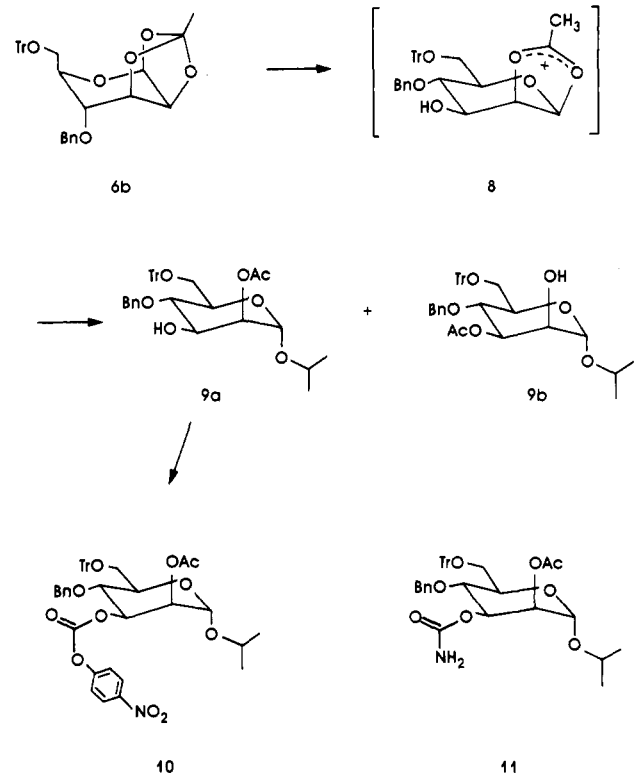
Of the methods available for the preparation of 1,2-*trans*-glycosides,[14] it has been shown that glycosidic bond formation in polar solvents such as nitromethane generally proceeds optimally when Hg(II) salts are employed as catalysts.[14f] However, in nonpolar solvents such as dichloroethane, pyridinium and lutidinium perchlorates are preferred[14a-c] and give better yields.[14d] Extensive studies by Kochetkov and others[14] have shown that glycosylations are catalyst-, solvent-, and temperature-dependent.

Isopropyl alcohol was chosen for initial model studies of glycosylation with tricyclic mannose derivative **6b** under conditions of lutidinium perchlorate catalysis. Treatment of **6b** with isopropyl alcohol under these conditions provided two major products in ~55% total yield; these were separated chromatographically and identified as isopropyl 2-*O*-acetyl-4-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (**9a**) and the 3-*O*-acetyl isomer (**9b**), having characteristic[15] ^1H NMR resonances for the acetyl groups at δ 2.20 and 2.02, respectively. When the crude reaction mixture was purified by chromatography on alumina, **9a** and **9b** were obtained in a 1:1 ratio. Purification by chromatography on silica gel, however, provided **9a** and **9b** in a 5:1 ratio, and analysis of the crude reaction mixture by ^1H NMR showed predominantly the presence of a single acetyl signal at δ 2.20, corresponding to **9a**. Thus, although the formation of a mixture of acetates as primary reaction products would not have been without precedent,[4] the accumulated results suggested that the reaction was proceeding regio- and stereoselectivity, i.e., primarily via 1,2-acetoxonium ion **8**. Formation of the 3-*O*-acetyl isomer **9b** appeared to result from acetyl migration during chromatography.[16,17]

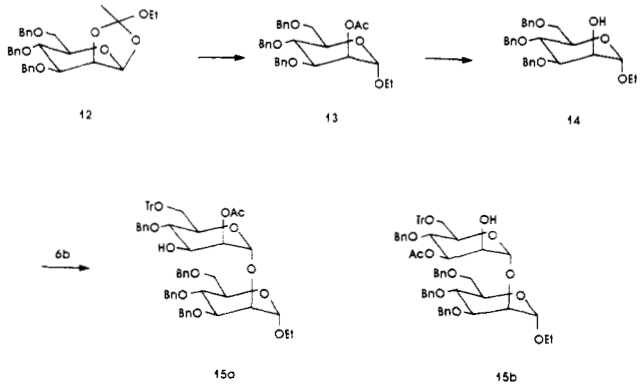


Having obtained **9a** in reasonable (45–52%) yields, it was of interest to investigate the preparation of 3-*O*-carbamoyl derivative **11** before proceeding further. Thus isopropyl glycoside **9a** was treated with *p*-nitrophenyl chloroformate[18] in pyridine to provide *p*-nitrophenyl carbonate derivative **10**: IR 1770 and 1745 cm^{-1}. Treatment of **10** with methanolic ammonia gave the expected 3-*O*-carbamoyl derivative **11** in 54% overall yield from **9a**: IR 3480, 3360, and 1740–1720 cm^{-1}. Having established that the requisite carbamoyl group could be introduced in good yield under mild conditions, glycosylation studies were continued using the more pertinent model ethyl mannopyranoside **14**.

The preparation of **14** was achieved starting from **4c** via the tri-*O*-benzylated ortho ester **12**. The latter was treated with anhydrous *p*-toluenesulfonic acid in dichloromethane;[19] deacetylation of crude **13** ($NaOCH_3$, 25 °C, 24 h) provided **14** in 83% overall yield from **4c**.

The coupling of **14** and **6b** provided a mixture of products from which disaccharides **15** could be isolated by preparative silica gel TLC. The yield of disaccharides (~20%) was disappointing and could not be improved by modification of the reaction conditions, such as change of

(13) Newman, M. S.; Chen, C. H. *J. Am. Chem. Soc.* **1973**, *95*, 278.
(14) (a) Kochetkov, N. K.; Bochkov, A. F.; Sokolovskaya, T. A.; Snyatkova, V. J. *Carbohydr. Res.* **1971**, *16*, 17. (b) Kochetkov, N. K.; Bochkov, A. F.; Yazlovetsky, I. G. *Carbohydr. Res.* **1969**, *9*, 49. (c) Kochetkov, N. K.; Bochkov, A. F. *Carbohydr. Res.* **1969**, *9*, 61. (d) Wulff, G.; Röhle, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 157. (e) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron Lett.* **1964**, 289. (f) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron* **1967**, *23*, 693.
(15) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 6098.
(16) Chacon-Fuertes, M. E.; Martin-Lomas, M. *Carbohydr. Res.* **1975**, *42*, C4.
(17) The formation of limited quantities of **9b** as a primary reaction product cannot be excluded and could occur via a 1,3-acetoxonium ion.[4]
(18) (a) Vaterlaus, B. P.; Kiss, J.; Spielberg, H. *Helv. Chim. Acta* **1964**, *47*, 381. (b) Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1973**, *5051*. (c) Omoto, S.; Takita, T.; Maeda, K.; Umezawa, S. *Carbohydr. Res.* **1973**, *30*, 239.
(19) (a) Francis, N. E.; Montgomery, R. *Carbohydr. Res.* **1968**, *3*, 511. (b) Francis, N. E.; Montgomery, R. *Carbohydr. Res.* **1968**, *6*, 286.



reaction temperature or catalyst. Although **15a** and **15b** could not be separated easily, analysis of the ^1H NMR spectrum indicated a 3:1 ratio of the 2-*O*-acetyl and 3-*O*-acetyl (**15a** and **15b**) disaccharides. The complex reaction mixture present prior to chromatographic purification and low yield of disaccharides **15** precluded ready identification of the source of **15b**, but did prompt us to investigate an alternate approach.

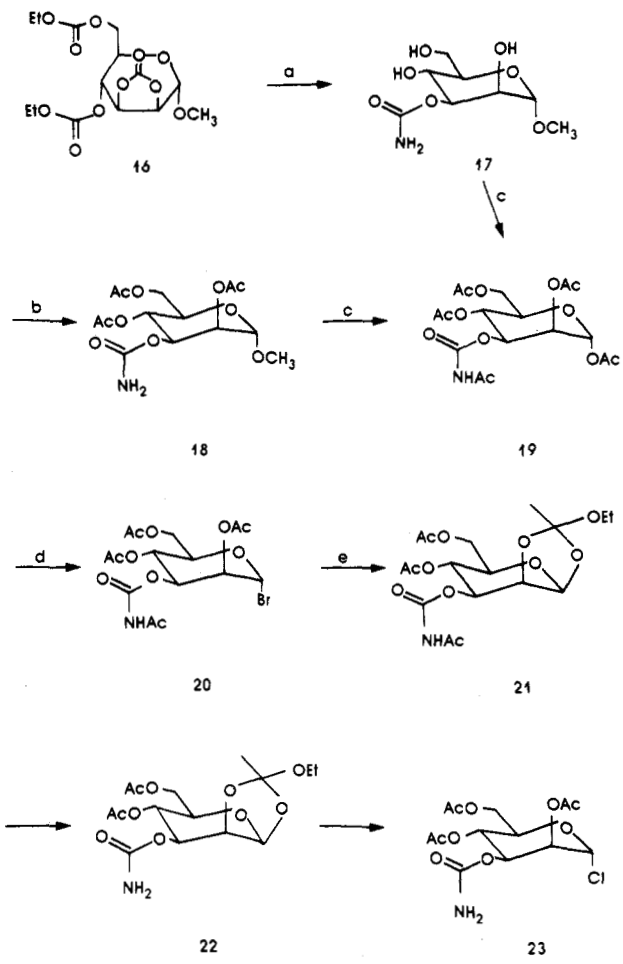
Reports by Hough and Priddle[20] and by Omoto et al.[18c] suggested the ready availability of 2,3-O-cyclic carbonate derivatives of methyl mannopyranoside (e.g., **16**) and their suitability as precursors for a 3-*O*-carbamoyl derivative of mannose via regioselective opening of the cyclic carbonate. The preparation of the known[18c] methyl 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranoside (**18**) was achieved by a modification of the published procedure involving direct ammonolysis of **16**[18c] (Scheme II). Acetylation of crude **17** and crystallization from isopropyl alcohol gave a sample of **18** having the same physical and spectroscopic properties as those reported. With our modified procedure, **18** could be prepared conveniently from methyl mannopyranoside on a multigram scale in 70–75% overall yield.

3-*O*-Carbamoylmannose derivative **18** was next employed as a potential substrate for conversion to ortho ester **22**, identified as a likely building block for elaboration of the carbohydrate moiety of bleomycin. Conversion of **18** to the anomeric acetate also resulted in *N*-acetylation of the carbamoyl group, to provide crystalline pentaacetate **19** in virtually quantitative yield.[21]

Several attempts were made to convert the methyl glycoside to a suitably reactive glycoside without concomitant N-acylation. The use of hydrochloric or hydrobromic acids, $SOCl_2$, $ZnBr_2/Cl_2CHOCH_3$,[22] or Lewis acids ($SnCl_4$, $TiCl_4$, $AlCl_3$)[4] provided either complex reaction mixtures or modification of the carbamoyl moiety. Treatment with trifluoroacetic anhydride in the presence of either sulfuric acid or trifuloromethanesulfonic acid resulted in extensive decomposition, while trifluoroacetic acid gave only N-acylation even at elevated temperatures.

To verify the validity of the overall approach to **22**, pentaacetate **19** was converted to 2,4,6-tri-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranosyl bromide (**20**),[2b] which was converted further to N-acetylated ortho ester **21**. Interestingly, an attempt to purify crude **21** by chromatography on alumina resulted in the isolation of a mixture of two products, one of which crystallized readily from ether. The ^1H NMR spectrum of the crystalline product reflected the presence of the ortho ester but lacked the (*N*-acetyl) signal at δ 2.37 present in authentic **21**. The

Scheme II[a]



[a] Reagents: (a) concentrated NH_4OH, EtOH; (b) Ac_2O, pyridine; (c) Ac_2O, concentrated H_2SO_4; (d) HBr/HOAc, CH_2Cl_2; (e) $(n\text{-}Bu)_4N^+Br^-$, EtOH, $(i\text{-}Pr)_2NEt$, CH_2Cl_2.

absence of this signal and the characteristic "amide" resonance at δ 7.94 suggested that alumina had effected selective N-deacetylation of **21** to provide **22**. As anticipated, the other product obtained from the alumina column was the expected triacetate **21**.[23]

The observation of (partial) alumina-mediated N-deacetylation of **21** during chromatographic purification prompted investigation of the conversion **21** → **22** in practical yields. Treatment of **21** with $NaOCH_3/CH_3OH$, followed by acetylation with Ac_2O/pyridine, gave mainly triacetate **4c**. Ammonolysis followed by acetylation gave a 1:1 mixture of **22** and **4c**, while treatment with aqueous $NaHCO_3$ (pH 8.5) in dioxane gave no reaction. When ortho ester **21** was treated with Lewis acids ($FeCl_3$, $AlCl_3$, $ZnCl_2$), complex mixtures were obtained. More successful was the use of alumina for batch deacetylation of **21**. When benzene solutions of **21** were stirred at 50 °C in the presence of basic activated alumina (pH ~10) or activated chromatographic grade alumina (MCB), crystalline ortho ester **22** could be obtained in yields as high as 80–85%.[24]

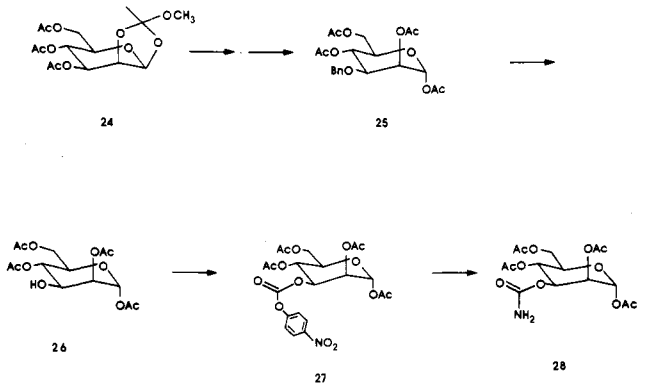
In addition to 3-*O*-carbamoylmannose derivatives **20–22**, another derivative of potential interest as a synthetic intermediate was prepared from **22** by treatment with trimethylsilyl chloride in dichloromethane at reflux. Crystalline 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-manno-

(20) Hough, L.; Priddle, J. E. *J. Chem. Soc.* **1961**, 3178.
(21) Compound **19** could also be obtained directly from **17** via treatment with sulfuric acid–acetic anhydride.
(22) Iversen, T.; Bundle, D. R. *Can. J.Chem.* **1982**, *60*, 299.
(23) Subsequent experimentation revealed that **21** could be purified by chromatography on silica gel with little concomitant N-deacylation.
(24) Better yields were generally obtained when the reaction mixture was acetylated with Ac_2O/pyridine following alumina treatment, to replace missing *O*-acetyl groups.

pyranosyl chloride (**23**) was obtained in excellent yield.[25] These four derivatives were subsequently employed for glycosylation studies and proved to be of utility for the synthesis of bleomycin.[1]

Although the derivatives identified above were found to be useful for the elaboration of bleomycin, an alternative route to mannopyranosyl chloride **23** was sought to preclude the introduction of the *N*-acetyl group on the carbamoyl moiety and thereby to simplify the overall synthesis.

Ponpipom[26] reported the synthesis of 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-α-D-mannopyranose (**25**) in ~40% overall yield from the readily available orthoacetate **24**[9,12] and also that hydrogenolysis of **25** gave 1,2,4,6-tetra-*O*-acetyl-α-D-mannopyranose (**26**). It was anticipated that activation of **26** with *p*-nitrophenyl chloroformate followed by ammonolysis would provide key intermediate 1,2,4,6-tetra-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranose (**28**), a logical precursor for **23**.



Accordingly, tetraacetate **25** was prepared in 78% overall yield from ortho ester **24** by slight modification of the published procedure.[26] Although this compound has been characterized previously it was of interest to establish unambiguously the position of the benzyl protecting group. This was accomplished by high-field ^{1}H NMR decoupling studies; H-3 was shown to resonate at δ 3.86, i.e., considerably upfield from a typical 3-*O*-acyl group, confirming that the benzyl group was, indeed, located at the 3-position of **25**.

Hydrogenolysis of **25** provided tetraacetate **26** in 86% yield; ^{1}H NMR analysis confirmed that none of the acetyl groups had migrated concomitant with debenzylation or purification.[16] Treatment of **26** with *p*-nitrophenyl chloroformate in the presence of catalytic (*N*,*N*-dimethylamino)pyridine provided *p*-nitrophenyl carbonate **27**, as judged by the downfield shift of H-3 in the ^{1}H NMR spectrum from δ 4.09 to 5.2. Treatment of **27** with methanolic ammonia provided only small amounts (<10%) of the desired product **28**, due to the predominant formation of peracetylmannose. However, the use of THF/ammonia afforded a single product having the same properties as an authentic sample of **28** prepared by acid catalyzed cleavage of ortho ester **22**; the two materials were shown to exhibit identical chromatographic behavior and to have the same ^{1}NMR spectra. Treatment of tetraacetate **28** with anhydrous hydrogen chloride in dry glyme provided 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl chloride (**23**) in 63% yield, after column chromatography, which crystallized as colorless needles from ether–hexane. This material was found to be identical in all respects with that obtained from ortho ester **22**.

(25) Newman, M. S.; Olson, D. R. *J. Org. Chem.* **1973**, *38*, 4203.
(26) Ponpipom, M. M. *Carbohydr. Res.* **1977**, *59*, 311.

Experimental Section

Melting points were taken on a Thomas Hoover apparatus and are not corrected.

1,2,4-*O*-Orthoacetyl-6-*O*-(triphenylmethyl)-α-D-glucopyranose (3a). A solution of 0.98 g (1.98 mmol) of 1,2-*O*-(1-ethoxyethylidene)-6-*O*-(triphenylmethyl)-α-D-glucopyranose (**2b**)[3] in 30 mL of dichloromethane was treated with 90 mg (0.5 mmol) of lutidinium hydrobromide over 4-Å molecular sieves at 25 °C for 6 days. The reaction mixture was filtered, and the filtrate was concentrated. The residue was partitioned between ether and water, and the ether extract was washed with saturated brine, then dried (Na_2SO_4), and concentrated to give a yellow oil. Purification was effected by chromatography on a column (1.8 × 16 cm) of activated alumina; elution was with 1:1 benzene–ethyl acetate and then with ethyl acetate. 1,2,4-*O*-Orthoacetyl-6-*O*-trityl-α-D-glucoyranose (**3a**) was obtained as a yellow foam (0.58 g, 65%) that crystallized from ether–pentane as colorless needles: mp 104–106 °C; ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.62 (s, 3), 3.31 (dd, 1, *J* = 10.7, 3.3 Hz), 3.71 (dd, 1, *J* = 10.7, 4.7 Hz), 4.07 (br d, 1), 4.10 (br s, 1) 4.43 (br d, 1, *J* = 4.8, <1 Hz), 4.63 (ddd, 1, *J* = 4.7, 3.3, <1 Hz), 5.91 (d, 1, *J* = 4.8 Hz), 7.23–7.45 (m, 15); IR (CCl_4) 3430, 3070, 2960, 1495, 1455, 1410, 1325, 1290, 1145, 1095, 1085, 1055, 895, 845, 710 cm^{-1}.

Anal. Calcd for $C_{27}H_{26}O_6 \cdot 0.5H_2O$: C, 71.18; H, 5.98. Found: C, 71.55; H, 5.92.

3-*O*-Acetyl-1,2,4-*O*-orthoacetyl-6-*O*-(triphenylmethyl)-α-D-glucopyranose (3b). 1,2,4-*O*-Orthoacetyl-6-*O*-trityl-α-D-glucopyranose (**3a**) (0.2 g, 0.45 mmol) was treated with 0.5 mL of acetic anhydride and 1.3 mL of diisopropylethylamine in 5 mL of ether at 25 °C for 24 h. The reaction mixture was diluted with 5 mL of ether and then washed with water, saturated aqueous $NaHCO_3$, and saturated brine. The ether layer was dried (Na_2SO_4) and concentrated to give a crystalline residue. Recrystallization from ether–pentane provided 3-*O*-acetyl-1,2,4-*O*-orthoacetyl-6-*O*-trityl-α-D-glucopyranose (**3b**) as colorless needles: mp 133–134 °C; ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.57 (s, 3), 1.70 (s, 3), 3.08 (dd, 1, *J* = 8.95, 8.7 Hz), 3.46 (dd, 1, *J* = 8.95, 6.4 Hz), 4.41 (dd, 1, *J* = 4.7, 2.2 Hz), 4.44 (dd, 1, *J* = 4.5, <1 Hz), 4.78 (ddd, *J* = 8.7, 6.4, <1 Hz), 5.12 (dd, 1, *J* = 4.5, 2.2 Hz), 5.76 (d, 1, *J* = 4.7 Hz), 7.22–7.44 (m, 15); IR (CCl_4) 1755, 1490, 1445, 1405, 1225, 1140, 1075, 1055, 880 cm^{-1}.

Anal. Calcd for $C_{29}H_{28}O_7$: C, 71.28; H, 5.78. Found: C, 71.14; H, 5.91.

General Procedure for the Preparation of 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-alkoxyethylidene)-β-D-mannopyranoses 4. A solution of 22.5 g (55 mmol) of 2,3,4,6-tetra-*O*-acetylmannopyranosyl bromide[27] in 40 mL of 1:1 $CHCl_3$–lutidine containing 1.5 g (4.6 mmol) of tetra-*n*-butyl ammonium bromide and 5.0–5.3 mL of the appropriate alcohol was stirred at 45 °C for 24 h. The cooled reaction mixture was diluted with 50 mL of ether, and the precipitate was removed by filtration. The filtrate was washed with water, saturated aqueous $NaHCO_3$, and saturated brine, then dried (Na_2SO_4), and concentrated. The residue was crystallized from 1:1 ethanol–water, affording the individual ortho esters in 16–70% yields (Table I).

Alternative Procedure for the Preparation of 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-isopropoxyethylidene)-β-D-mannopyranose (4b). A solution containing 4.11 g (10 mmol) of 2,3,4,6-tetra-*O*-acetylmannopyranosyl bromide in 50 mL of dichloromethane was cooled to −10 °C and treated with 1.76 g (10 mmol) of *N*,*N*-dimethylformamide diisopropyl acetal and 2.57 g (10 mmol) of silver trifluoromethanesulfonate. The reaction mixture was stirred at −10 °C for 15 min and filtered through a pad of Celite and activated charcoal, and the filtrate was washed with saturated aqueous $NaHCO_3$ (50 mL). The yellow solution was dried (Na_2SO_4) and concentrated, and the residue was crystallized from 1:1 ethanol–water to provide **4b** as colorless needles, yield 2.60 g (66%), mp 85–87 °C. This material was found to be the same in all respects as that prepared by the general procedure outlined above.

General Procedure for the Preparation of 1,2-*O*-(1-Alkoxyethylidene)-6-*O*-(triphenylmethyl)-β-D-mannopyranoses (5). Triacetylated mannopyranoses **4** (0.4 M solution in methanol)

(27) Lemieux, R. U. *Methods Carbohydr. Chem.* **1963**, *2*, 221.

were treated with sodium methoxide (0.42 M final concentration) at 25 °C for 12 h. The reaction mixture was concentrated, and the residue was dried for several hours under vacuum. The resulting ortho esters were dissolved in dry DMF (to provide a 0.4 M solution), treated with diisopropylethylamine (3.5 equiv), and stirred over 4-Å molecular sieves for 48 h. Trityl chloride (1.5 equiv) was added, and the reaction mixture was stirred at 25 °C for an additional 24 h. The resulting turbid solution was washed with water and saturated brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on activated alumina; elution with 1:1 benzene–ethyl acetate, followed by 10–15% methanol in $CHCl_3$, provided tritylated mannopyranoses **5** in 42–86% yields (Table II).

1,2,3-*O*-Orthoacetyl-6-*O*-(triphenylmethyl)-β-D-mannopyranose (6a). Method A. A solution of 2.71 g (5.5 mmol) of 1,2-*O*-(1-ethoxyethylidene)-6-*O*-trityl-β-D-mannopyranose (**5c**) in 100 mL of dichloromethane was treated with 0.2 g of triphenylmethyl chloride in the presence of 4-Å molecular sieves at reflux for 72 h. The reaction mixture was filtered, and the filtrate was concentrated under diminished pressure. The residue was purified by chromatography on a column of activated alumina (2.5 × 20 cm); elution was with 1:1 benzene–ethyl acetate, to remove less polar byproducts, and then with ethyl acetate. 1,2,3-*O*-Orthoacetyl-6-*O*-trityl-β-D-mannopyranose (**6a**) was obtained as a colorless foam: yield, 1.1 g (43%); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.48 (s, 3), 1.92 (d, 1, J = 4.65 Hz, exchangeable with D_2O), 3.43 (dd, 1, J = 9.35, 5.3 Hz), 3.63 (dd, 1 J = 9.4, 9.35 Hz), 4.04 (ddd, 1, J = 9.4, 5.3, <1 Hz), 4.17 (m, 1), 4.47 (br t, 1), 4.66 (br t, 1), 5.46 (br t, 1), 7.21–7.46 (m, 15). Additional information was obtained by decoupling experiments: irradiation of the signal at δ 4.17 caused the signal at δ 4.47 to collapse to a doublet (J = 4.4 Hz, addition of D_2O caused the doublet to collapse to a singlet) and the signal at δ 4.66 to collapse to a doublet (J = 2.9 Hz). Also changed by irradiation at δ 4.17 was the signal at δ 5.46, which collapsed to a doublet (J = 2.6 Hz). IR (CCl_4) 3690, 3480, 3030, 2940, 1490, 1450, 1430, 1310, 1155, 1130, 710 cm^{-1}.

Anal. Calcd for $C_{27}H_{26}O_6 \cdot 0.5H_2O$: C, 71.18; H, 5.98. Found: C, 70.90; H, 5.94.

Method B. A solution of 0.45 g (0.87 mmol) of 1,2-*O*-(1-*tert*-butoxyethylidene)-6-*O*-trityl-β-D-mannopyranose (**5a**) in 15 mL of dichloromethane was treated with 45 mg (0.24 mmol) of lutidinium hydrobromide in the presence of 4-Å molecular sieves at 25 °C for 6 days. The reaction mixture was filtered, and the filtrate was concentrated under diminished pressure. Purification of the residue was accomplished by chromatography on alumina (1.3 × 21 cm column); elution was with 1:1 benzene–ethyl acetate and then with ethyl acetate. Tritylated mannopyranose **6a** was obtained as a colorless foam, yield 0.22 g (57%). This material was identical in all respects with the sample of **6a** prepared from ethoxyethylidene derivative **5c**.

4-*O*-Benzyl-1,2,3-*O*-orthoacetyl-6-*O*-(triphenylmethyl)-β-D-mannopyranose (6b). A solution of 0.22 g (0.5 mmol) of 1,2,3-*O*-orthoacetyl-6-*O*-trityl-β-D-mannopyranose (**6a**) in 10 mL of dry glyme was cooled to 0 °C and treated with 60 mg (2.5 mmol) of sodium hydride. The reaction mixture was stirred at 0 °C for 30 min, then treated with 0.43 g (2.5 mmol) of benzyl bromide, and allowed to warm to room temperature. After an additional 24 h of stirring, the reaction mixture was cooled to 0 °C and treated dropwise with 0.5 mL of methanol. The reaction mixture was then diluted with ether, washed with water and saturated brine, and then dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography on a column (1.3 × 15 cm) of activated alumina; elution with 1:1 hexane–benzene afforded 4-*O*-benzyl-1,2,3-*O*-orthoacetyl-6-*O*-trityl-β-D-mannopyranose (**6b**) as a colorless foam: yield, 0.25 g (94%); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.49 (s, 3), 3.44 (dd, 1, J = 9.1, 5.0 Hz), 3.67 (dd, 1, J = 9.6, 9.1 Hz), 4.15–4.24 (m, 3), 4.62 (d, 1, J = 12.2 Hz), 4.65 (br t, 1, collapsed to a doublet (J = 3.1 Hz) upon irradiation at δ 5.48 and a doublet (J = 2.5 Hz) when irradiated at δ 4.20), 4.76 (d, 1, J = 12.2 Hz), 5.48 (br t, 1, collapsed to a doublet (J = 2.5 Hz) upon irradiation at δ 4.20 and a broad singlet when irradiated at δ 4.65), 7.24–7.46 (m, 20).

Reaction of 6b with Isopropyl Alcohol. A solution of 243 mg (0.45 mmol) of 4-*O*-benzyl-1,2,3-*O*-orthoacetyl-6-*O*-trityl-β-D-mannopyranose (**6b**) in 5 mL of dry 1,2-dichloroethane was treated with 90 mg (1.5 mmol) of isopropyl alcohol and 2 mg of lutidinium perchlorate. The reaction mixture was heated at reflux for 2 h, then cooled, diluted with 10 mL of dichloromethane, and washed with saturated aqueous $NaHCO_3$. The dried (Na_2SO_4) organic layer was concentrated, and the residue was purified by preparative silica gel TLC, development with 3:1 benzene–ethyl acetate. Isopropyl 2-*O*-acetyl-4-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside (**9a**) was isolated as a colorless foam: yield, 120 mg (45%); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.18 (d, 3), 1.21 (d, 3), 2.22 (s, 3), 3.24 (dd, 1, J = 10.0, 2.9 Hz), 3.56 (dd, 1, J = 10.0, <1 Hz), 3.86 (m, 1), 3.97 (m, 2), 4.14 (m, 1), 4.25 (d, 1, J = 10.7 Hz), 4.55 (d, 1, J = 10.7 Hz), 5.03 (br s, 1), 5.07 (m, 1), 7.21–7.54 (m, 20).

Isopropyl 2-*O*-Acetyl-4-*O*-benzyl-3-*O*-carbamoyl-6-*O*-(triphenylmethyl)-α-D-mannopyranoside (11). A solution of 123 mg (0.21 mmol) of isopropyl 2-*O*-acetyl-4-*O*-benzyl-6-*O*-(triphenylmethyl)-α-D-mannopyranoside (**9a**) in 10 mL of dry pyridine was treated with 80 mg (0.4 mmol) of *p*-nitrophenyl chloroformate at 25 °C for 18 h. The reaction mixture was diluted with 50 mL of benzene and washed successively with 0.5 M aqueous H_2SO_4 (5 × 20 mL), saturated aqueous $NaHCO_3$ (5 × 20 mL), and water (2 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue was effected by preparative silica gel TLC, development with 1:1 hexane–ether. Isopropyl 2-*O*-acetyl-4-*O*-benzyl-3-*O*-[(*p*-nitrophenoxy)carbonyl]-6-*O*-trityl-α-D-mannopyranoside (**10**) was isolated as a colorless foam: yield, 95 mg (60%); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.14 (d, 3), 1.26 (d, 3), 2.26 (s, 3), 3.15–3.77 (m, 2), 3.82–4.71 (m, 5), 5.00–5.30 (m, 3), 6.82 (d, 2), 7.05–7.58 (m, 20), 8.08 (m, 2); IR (Nujol) 1770, 1745, 1590, 1525, 1490, 1380, 1350, 1260, 1210, 1080 cm^{-1}.

A solution of 95 mg (0.13 mmol) of **10** in 5 mL of dichloromethane was treated with 5 mL of 1 M methanolic ammonia at 25 °C for 4 h. The reaction mixture was concentrated, and the crude product was dissolved in 50 mL of dichloromethane and washed with 0.5 M aqueous Na_2CO_3 (3 × 20 mL) and water (2 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under diminished pressure. Isopropyl 2-*O*-acetyl-4-*O*-benzyl-3-*O*-carbamoyl-6-*O*-trityl-α-D-mannopyranoside (**11**) was obtained as a white solid: yield, 71 mg (54% from **9a**); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.18 (d, 3), 1.21 (d, 3), 2.22 (s, 3), 3.22 (dd, 1, J = 9.9, 3.7 Hz), 3.55 (dd, 1, J = 9.9, <1 Hz), 3.90–4.07 (m, 3), 4.16 (d, 1, J = 10.7 Hz), 4.42 (d, 1, J = 10.7 Hz), 4.60 (br s, 2, exchangeable with D_2O), 5.00 (br s, 1), 5.21 (m, 1), 5.28 (dd, 1, J = 9.4, 3.1 Hz), 7.19–7.54 (m, 20).

3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (12). A solution of 3.8 g (10 mmol) of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**4c**) in 100 mL of methanol was treated with 0.27 g (5 mmol) of sodium methoxide in 5 mL of methanol. The combined solution was maintained at 25 °C for 16 h and then concentrated under diminished pressure. The residue was dissolved in 50 mL of dry 1,2-dimethoxyethane, and the resulting solution was cooled to 0 °C and then treated with 1.5 g (62 mmol) of sodium hydride. The reaction mixture was stirred at 0 °C for 20 min and then treated with 8.35 g (50 mmol) of benzyl bromide. The reaction mixture was stirred under N_2 at 25 °C for 24 h, then cooled to 0 °C, and treated with 4 mL of methanol. Stirring was continued for an additional 2 h at 25 °C, and the reaction mixture was then diluted with 50 mL of ether, washed with saturated brine (50 mL), and dried (Na_2SO_4). Concentration of the dried organic phase afforded a residue that was purified by chromatography on a column (3 × 20 cm) of activated alumina. The column was washed with benzene and then with 1:1 benzene–ethyl acetate to provide the desired product. 3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**12**) crystallized from ether–pentane as colorless needles: yield, 5.12 g (98%); mp 85–86 °C; ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.20 (t, 1), 1.76 (s, 3), 3.53 (q, 2), 3.62–4.20 (m, 5), 4.35 (t, 1, J = 3.5 Hz), 4.43–5.04 (m, 6), 5.30 (d, 1, J = 3.5 Hz), 7.25–7.40 (m, 15).

Anal. Calcd for $C_{31}H_{36}O_7$: C, 71.50; H, 6.97. Found: C, 71.96; H, 6.95.

Ethyl 3,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (14). A solution of 1.04 g (2 mmol) of 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**12**) and 35 mg of anhydrous *p*-toluenesulfonic acid in 5 mL of dichloromethane was heated at reflux for 2 h. The cooled reaction mixture was diluted with 20 mL of dichloromethane and washed with saturated aqueous

$NaHCO_3$. The dried (Na_2SO_4) dichloromethane phase was concentrated to afford ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**13**) as a colorless syrup: ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.16 (t, 3), 2.14 (s, 3), 3.25–4.20 (m, 7), 4.30–5.04 (m, 7), 5.38 (m, 1), 7.20–7.40 (m, 15).

The syrup was dissolved in 10 mL of methanol and treated with 15 mg of sodium methoxide at 25 °C for 24 h. The reaction mixture was concentrated, and the crude product was purified by chromatography on an alumina column (2.5 × 20 cm). Elution of the column with ethyl acetate provided ethyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**14**), which was isolated as a colorless syrup: yield, 0.82 g (85%); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.17 (t, 3), 2.76 (br s, 1, exchangeable with D_2O), 3.22–4.09 (m, 7), 4.30–4.82 (m, 7), 4.87 (m, 1), 7.20–7.38 (m, 15); IR ($CHCl_3$) 3560, 3020, 2915, 1490, 1450, 1360, 1205, 1100, 1056, 780 cm^{-1}.

Reaction of 6b with Ethyl 3,4,6-Tri-*O*-benzyl-α-D-mannopyranoside (14). A solution of 204 mg (0.38 mmol) of 4-*O*-benzyl-1,2,3-*O*-orthoacetyl-6-*O*-trityl-β-D-mannopyranose (**6b**) in 5 mL of dry 1,2-dichloroethane was treated with 370 mg (0.77 mmol) of ethyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**14**) and 2 mg of lutidinium perchlorate. The reaction mixture was heated at reflux for 2 h, then cooled, diluted with 15 mL of dichloromethane, and washed with saturated aqueous $NaHCO_3$. The dried (Na_2SO_4) organic layer was concentrated, and the residue was purified by preparative silica gel TLC, development with 8% ethyl acetate in benzene. Disaccharides **15** were isolated as a colorless syrup in a total yield of 85 mg (22%): ^1H NMR (of **15a**) ($CDCl_3$, $(CH_3)_4Si$) δ 1.11 (t, 3, J = 7.0 Hz), 2.19 (s, 3), 3.23 (dd, 1, J = 10.0, 4.5 Hz), 3.34 (dd, 1, J = 9.5, 7.1 Hz), 3.57 (dd, 1, J = 10.0, <1 Hz), 3.62–3.78 (m, 4), 3.84 (m, 2), 3.93 (m, 1), 3.97 (dd, 1, J = 9.4, 2.6 Hz), 4.15–4.20 (m, 2), 4.21 (d, 1, J = 10.9 Hz), 4.47–4.88 (m, 7), 4.93 (br s, 1), 5.27 (d, 1, J = 1.5 Hz), 5.31 (dd, 1, J = 2.8, 1.5 Hz), 6.94–7.52 (m, 35); IR ($CHCl_3$) 3580, 3040, 2930, 1740, 1595, 1490, 1450, 1420, 1370, 1240, 1180, 910 cm^{-1}.

Methyl 2,4,6-Tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranoside (18). Compound **18** was synthesized by the method of Omoto et al.[18c] in 70–75% overall yield from commercially available methyl mannopyranoside.

Anal. Calcd for $C_{14}H_{21}NO_{10}$: C, 46.27; H, 5.83. Found: C, 45.99; H, 5.78.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranose (19). To 1.0 g (2.75 mmol) of methyl 2,4,6-tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranoside (**18**) in 5 mL of acetic anhydride was added 20 mL of 2% H_2SO_4 in acetic anhydride. The reaction mixture was maintained at 25 °C for 2 h, then diluted with 100 mL of $CHCl_3$, and washed successively with an ice–water mixture (2 × 150 mL), saturated aqueous $NaHCO_3$ (2 × 150 mL), and water (2 × 150 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was crystallized from absolute ethanol to provide 1,2,4,6-tetra-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranose (**19**) as colorless microcrystals, yield 1.15 g (96%). Recrystallization from absolute ethanol afforded an analytically pure sample: mp 135–136 °C; $[\alpha]^{25}_D$ + 23.3° (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.08 (s, 3), 2.10 (s, 3), 2.18 (s, 6), 2.41 (s, 3), 4.07 (m, 1), 4.11 (dd, 1, J = 12.3, 2.3 Hz), 4.29 (dd, 1, J = 12.3, 4.6 Hz), 5.24–5.40 (m, 3), 6.11 (d, 1, J = 1.6 Hz), 7.46 (br s, 1, exchangeable with D_2O).

Anal. Calcd for $C_{17}H_{23}NO_{12}$: C, 47.09; H, 5.35. Found: C, 46.87; H, 5.31.

4,6-Di-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (21). A solution of 0.80 g (1.85 mmol) of 1,2,4,6-tetra-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranose (**19**) in 15 mL of dichloromethane was treated with 10 mL of 32% HBr in acetic acid at 25 °C for 2 h. The reaction mixture was diluted with 50 mL of dichloromethane and washed successively with an ice–water mixture (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and water (2 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated to provide crude 2,4,6-tri-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranosyl bromide (**20**) as a colorless foam: yield, 0.75 g (89%); $[\alpha]^{25}_D$ + 78.2° (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.10 (s, 6), 2.16 (s, 3), 2.40 (s, 3), 3.98–4.45 (m, 3), 5.10–5.90 (m, 3), 6.29 (br s, 1), 8.00–8.40 (br d, 1).

A solution of crude bromide **20** (0.75 g, 1.64 mmol) in 8 mL of dichloromethane was treated with 0.41 g (3.15 mmol) of diisopropylethylamine, 0.12 g (2.6 mmol) of anhydrous ethanol, and 0.13 g (0.4 mmol) of tetrabutylammonium bromide at reflux for 13 h. The reaction mixture was cooled, diluted with 50 mL of dichloromethane, and washed with water (2 × 50 mL) and saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue was accomplished by chromatography on a silica gel column (2.8 × 20 cm); elution with 6:4 hexane–ethyl acetate containing 1% triethylamine provided 4,6-di-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-1,2-*O*-(1-ethoxyethylidene)-α-D-mannopyranose (**21**) as a colorless syrup: yield, 0.33 g (43%); $[\alpha]^{25}_D$ −25.5° (*c* 2.51, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.17 (t, 3, J = 7.0 Hz), 1.72 (s, 3), 2.05 (s, 6), 2.37 (s, 3), 3.54 (m, 2), 3.69 (ddd, 1, J = 9.7, 4.8, 2.5 Hz), 4.13 (dd, 1, J = 12.2, 2.5 Hz), 4.22 (dd, 1, J = 12.2, 4.8 Hz), 4.64 (dd, 1, J = 4.0, 2.4 Hz), 5.07 (dd, 1, J = 9.9, 4.0 Hz), 5.27 (dd, 1, J = 9.9, 9.7 Hz), 5.50 (d, 1, J = 2.4 Hz), 7.94 (br s, 1, exchangeable with D_2O).

Anal. Calcd for $C_{17}H_{25}NO_{11}$: C, 48.67; H, 6.01. Found: C, 48.77; H, 6.05. Also obtained from the silica gel column was 76 mg (11%) of 4,6-di-*O*-acetyl-3-*O*-carbamoyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**22**), mp 163–165 °C.

4,6-Di-*O*-acetyl-3-*O*-carbamoyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (22). A solution of 0.24 g (0.57 mmol) of 4,6-di-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose in 25 mL of benzene was stirred and heated at 50 °C with 1.0 g of activated alumina (MCB chromatographic grade) for 20 h. The cooled reaction mixture was filtered through Celite, the Celite was washed with 100 mL of 1:1 ethyl acetate–methanol, and the combined filtrate was concentrated. The residue was treated with 30 mL of 2:1 pyridine–acetic anhydride at 25 °C for 4 h. The reaction was quenched by addition of ice, and the resulting solution was concentrated under diminished pressure; codistillation of portions of toluene facilitated removal of pyridine and acetic acid. The residue was partitioned between dichloromethane (20 mL) and water (10 mL), and the organic phase was washed with water (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in ether; 4,6-di-*O*-acetyl-3-*O*-carbamoyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**22**) crystallized as colorless needles, yield 0.18 g (83%). Recrystallization from ether provided an analytically pure sample: mp 163–165 °C; $[\alpha]^{25}_D$ −13.7° (*c* 1.90, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.19 (t, 3, J = 7.0 Hz), 1.76 (s, 3), 2.07 (s, 6), 3.58 (m, 2), 3.68 (ddd, 1, J = 9.7, 4.8, 2.5 Hz), 4.14 (dd, 1, J = 12.4, 2.5 Hz), 4.24 (dd, 1, J = 12.4, 4.8 Hz), 4.62 (dd, 1, J = 3.9, 2.4 Hz), 5.07 (dd, 1, J = 10.0, 3.9 Hz), 5.29 (dd, 1, J = 10.0, 9.7 Hz), 5.48 (d, 1, J = 2.4 Hz); IR (Nujol) 3450, 3370, 3320, 1755–1720, 1600, 1460, 1370, 1250, 1030 cm^{-1}.

Anal. Calcd for $C_{15}H_{23}NO_{10}$: C, 47.73; H, 6.15. Found: C, 47.44; H, 6.17.

2,4,6-Tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl Chloride (23). A solution of 1.5 g (4.0 mmol) of 3-*O*-carbamoyl-4,6-di-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose (**22**) and 1.28 g (11.8 mmol) of freshly distilled chlorotrimethylsilane in 10 mL of dichloromethane was heated at reflux for 3 h. The cooled reaction mixture was concentrated to give a colorless foam, which crystallized from ether–hexane. 3-*O*-Carbamoyl-2,4,6-tri-*O*-acetyl-α-D-mannopyranosyl chloride was obtained as colorless needles: yield, 1.36 g (93%); mp 132–134 °C; $[\alpha]^{25}_D$ +83.6° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.09 (s, 3), 2.11 (s, 3), 2.18 (s, 3), 4.14 (dd, 1, J = 12.1, 1.4 Hz), 4.28 (ddd, 1, J = 10.0, 5.0, 1.4 Hz), 4.33 (dd, 1, J = 12.1, 5.0 Hz), 4.70 (br s, 2, exchangeable with D_2O), 5.34 (dd, 1, J = 10.2, 10.0 Hz), 5.40 (dd, 1, J = 3.4, <1 Hz), 5.52 (dd, 1, J = 10.2, 3.4 Hz), 6.00 (br s, 1).

1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzylmannopyranose (25): ^1H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.02 (s, 3), 2.08 (s, 3), 2.12 (s, 3), 2.16 (s, 3), 3.86 (dd, 1, J = 9.7, 3.3 Hz), 3.93 (ddd, 1, J = 9.9, 5.2, 2.3 Hz), 4.08 (dd, 1, J = 12.4, 2.3 Hz), 4.23 (dd, 1, J = 12.4, 5.2 Hz), 4.44 (d, 1, J = 12.1 Hz), 4.68 (d, 1, J = 12.1 Hz), 5.28 (dd, 1, J = 9.9, 9.7 Hz), 5.35 (dd, 1, J = 3.3, 1.8 Hz), 6.09 (d, 1, J = 1.8 Hz), 7.25–7.36 (m, 5).

1,2,4,6-Tetra-*O*-acetyl-α-D-mannopyranose (26). 3-*O*-Benzylmannose derivative **25**[26] (225 mg, 0.51 mmol) in 3 mL of ethyl acetate was hydrogenated (1 atm of H_2) over 100 mg of 10% palladium-on-carbon at 25 °C for 14 h. The reaction mixture was diluted with ethanol, filtered through a Celite pad, and concentrated. Purification of the residue by flash column chromatog-

raphy[28] (5-g column, elution with 20% ethyl acetate in hexane) provided 1,2,4,6-tetra-*O*-acetyl-α-D-mannopyranose (**26**) as a colorless syrup: yield, 154 mg (86%); ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.07 (s, 3), 2.12 (s, 3), 2.13 (s, 3), 2.18 (s, 3), 2.53 (br d, 1, exchangeable with D_2O), 3.97 (m, 1), 4.09 (m, 2), 4.28 (dd, 1, J = 12.3, 4.9 Hz), 5.08 (m, 2), 6.10 (d, 1, J = 1.4 Hz).

1,2,4,6-Tetra-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranose (28). Method A. A solution of tetraacetate **26** (154 mg, 0.44 mmol) in 20 mL of pyridine containing 2 mg of (*N*,*N*-dimethylamino)pyridine was treated with 175 mg (0.87 mmol) of *p*-nitrophenyl chloroformate. The reaction mixture was stirred at 25 °C for 20 h and then diluted with 150 mL of benzene and washed successively with portions of 0.5 M H_2SO_4, saturated aqueous $NaHCO_3$, and water. The dried (Na_2SO_4) solution was concentrated to afford the 3-*O*-*p*-nitrophenyl carbonate derivative **27** as a pale yellow syrup: ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.06 (s, 6), 2.13 (s, 3), 2.16 (s, 3), 4.00–4.48 (m, 3), 5.13–5.64 (m, 3), 6.17 (d, 1, J = 1.5 Hz), 7.45 and 8.30 (m, 4).

The syrup was dissolved in 12 mL of dichloromethane and treated with 4 mL of tetrahydrofuran that had been saturated with ammonia. The combined solution was maintained at 25 °C for 14 h, then concentrated, and purified by flash chromatography[28] (10-g silica gel column; elution was with 1:1 hexane–ethyl acetate). 1,2,4,6-Tetra-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranose (**28**) was obtained as a colorless syrup: ^{1}H NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.06 (s, 3), 2.08 (s, 3), 2.16 (s, 3), 2.17 (s, 3), 4.03 (m, 1), 4.08 (dd, 1, J = 12.2, 2.3 Hz), 4.28 (dd, 1, J = 12.2, 4.7 Hz), 4.79 (br s, 2, exchangeable with D_2O), 5.23–5.36 (m, 3), 6.08 (d, 1, J = 1.3 Hz).

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Anal. Calcd for $C_{15}H_{21}NO_{11}$: C, 46.02; H, 5.41. Found: C, 46.03; H, 5.57.

Method B. Ortho ester **22** (28 mg, 0.075 mmol) was dissolved in 1 mL of glacial acetic acid and stirred at 25 °C for 14 h. The solution was concentrated (codistillation with portions of toluene) and the residue was treated with 1.5 mL of 2:1 pyridine–acetic anhydride at 25 °C for 2 h. The reaction mixture was treated with ice, and the solution was concentrated to provide mannose derivative **28** as a colorless syrup, yield 22 mg (88%). This material was identical (silica gel TLC, ^{1}H NMR) with the material obtained by method A.

2,4,6-Tri-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranosyl Chloride (23). 1,2,4,6-Tetra-*O*-acetyl-3-*O*-carbamoyl-α-D-mannopyranose (**28**) (210 mg, 0.54 mmol) in 5 mL of dry dimethoxyethane was treated with anhydrous hydrogen chloride at −10 °C for 20 min. The reaction flask was stoppered tightly, and the reaction mixture was maintained at 25 °C for an additional 24 h. The solution was concentrated, and the residue was purified by flash chromatography[28] on silica gel (10-g column, elution with 1:1 hexane–ethyl acetate). Mannopyranosyl chloride **23** was obtained as a colorless syrup, yield 125 mg (63%). Crystallization of the syrup from ether–hexane provided **23** as colorless needles, mp 131–133 °C (no mp depression on admixture with a sample of **23** derived from **22**).

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Di-π-methane Rearrangements of Highly Sterically Congested Molecules: Inhibition of Free-Rotor Energy Dissipation. Mechanistic and Exploratory Organic Photochemistry[1,2]

Howard E. Zimmerman* and David N. Schissel

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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Four highly sterically congested di-π-methane reactants were synthesized and their photochemistry was studied. These were 1,1,5,5-tetraphenyl-3,3-diisopropyl-1,4-pentadiene (**1**), 1,1,5,5-tetraphenyl-3-isopropyl-3-methyl-1,4-pentadiene (**2**), 1,1-dimesityl-5,5-diphenyl-3,3-dimethyl-1,4-pentadiene (**3**), and 1,1,5,5-tetraphenyl-2,3,3,4-tetramethyl-1,4-pentadiene (**4**). Diene **4** was unreactive, and evidence was obtained for rapid singlet energy dissipation. Dienes **1**, **2**, and **3** exhibited normal singlet reactivity despite the severe steric congestion. Interestingly, a remarkable enhancement in triplet reactivity was encountered for the diisopropyl diene **1** and the dimesityl diene **3**. In contrast to the prototype 1,1,5,5-tetraphenyl-3,3-dimethyl-1,4-pentadiene (**28**) whose efficiency was known to be 0.0047, the triplet quantum efficiency for diene **1** was 0.018 and that for diene **3** was 0.043. Molecular mechanics was employed to correlate steric effects with the observed photochemistry.

An interesting facet of the di-π-methane rearrangement[3] of acyclic 1,4-dienes is the observation[3b,4b] that the triplet excited states are generally unreactive. This lack of reactivity has been ascribed to a "free-rotor effect"[4] in which a double bond twists with intersystem crossing to ground state and dissipation of excitation energy. However, there are exceptions to the generalization, so that some acyclic di-π-methane systems do exhibit triplet reactivity. Among these exceptions are molecules with substitution by phenyl and other delocalizing groups on the central carbon.[5] It seemed that this enhancement of reactivity might arise from delocalization effects by substituents on the central carbon or, instead, from steric congestion inhibiting free rotation. We wished to investigate acyclic di-π-methane systems incorporating bulky groups to determine if triplet

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