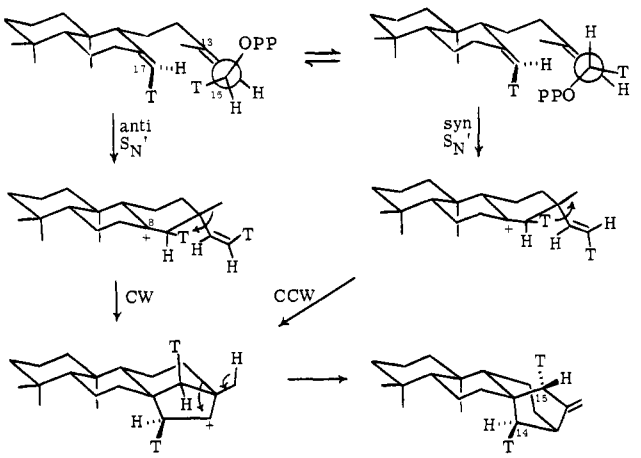
Scheme III



from (*S*)-**1**-*1-t* resides in the 14β position and that C-15 of **2** has undergone net inversion of configuration in the enzymatic cyclization.[16]

Copalyl pyrophosphate (**2**) labeled with tritium at C-17 in the anti-(*E*) configuration was prepared in order to reveal the stereochemistry of the cyclization, at this position. Methyl copalate[17] was converted to (*E*)-17-bromocopalol in three steps (32%),[18] and the corresponding tetrahydropyranyl ether was metallated with *n*-butyl- or *tert*-butyllithium (1:1 ether/THF, -20 to -30 °C, 1 h). Hydrolysis of the lithium derivative with tritiated water or deuterium oxide (-30 to 25 °C) followed by methanolysis to remove the protecting group afforded (*E*)-copalol-*17-t* and (*E*)-copalol-*17-d* (70-90% d_1): NMR ($CDCl_3$) δ 4.46 (s, 1 H, *syn*-C=CH_2), 4.76 (s, 0.1-0.3 H, *anti*-C=CH_2).[19,20] (*E*)-Copalyl pyrophosphate-*17-t* (0.65 mCi/mmol) was prepared[7a] and incubated with the enzyme extract from *M. macrocarpus* in four separate runs (0.5 M PO_4 buffer, pH 6.6, 2 mM $MgCl_2$, 5.5 mg of lyophilisate/mL). The kaurene-*15-t* was isolated, diluted, and recrystallized (10-27% incorporation, 0.36-0.45 μCi/mmol).

The location of the label in kaurene-*15-t* was determined by stereoselective exchange of the exo hydrogen at C-15 in 17-norkauranon-16-one (**7**). Base-catalyzed deuterium exchange (1 M NaOD, 1:2.7 v/v D_2O/dioxane, 22 °C) for 1 day and 19.5 days gave deuterated ketones having $d_0/d_1/d_2$ ratios of 3:97:0 and 3:73:24, respectively. Thus, the exo hydrogen underwent exchange ca. 200 times faster than the endo.[21] The exo assignment of the deuterium in **7**-d_1 was confirmed by reduction with sodium borohydride to 17-norkauran-16α-ol-*15*β-*d*: NMR ($CDCl_3$) δ 4.27 (br t, 1 H, J = ~5 Hz, C*H*OH). Norkauranone-*15*β-*t* was prepared in a similar manner, and the half-life for loss of radioactivity by exchange (1 M NaOH, 1:2.7 v/v H_2O dioxane, 22 °C) was estimated to be about 11 h. That is, one 17-h exchange decreased the radioactivity by 61-66%, and two such 17-h exchanges resulted in the loss of 84-94% of the tritium.

Oxidation (RuO_2, $NaIO_4$, H_2O/CCl_4/acetone, 25 °C) of the four biosynthetic samples of kaurene-*15-t* gave **7** (mp 111 °C, 43-55%, 0.27-0.57 mCi/mmol), following crystallization and sublimation. However, when subjected to one or two 17-h exchanges under the standard conditions, the recovered norkauranone-*15-t* retained essentially all [(92-111) ± (2-3%)] of its radioactivity. That the tritium was indeed situated in the endo position at C-15 was confirmed by condensation of **7** with ethyl formate (NaH, THF, 25 °C) to give the α-hydroxymethylene ketone **8** (mp 130-131 °C), which had lost (81-95) ± 7% of the radioactivity. We conclude that bond formation between C-13 and C-17 in the enzymatic cyclization of **2** occurs on the *si* (β) face of C-17.

Although these labeling experiments are sufficient to define the stereochemistry of the formation of ring C, there remain two stereochemically distinct pathways according to the biogenesis in Scheme I that would be consistent with overall inversion at C-15 (Scheme III). Thus, the combinations of either anti-S_N' attack of C-17 on C-13 of the allylic pyrophosphate with a clockwise (positive) rotation[22] of the vinyl group or syn-S_N' attack with counterclockwise (negative) rotation establish the *R* configuration in kaurene-*14-t*, it being assumed that bonding at C-8 occurs to the leading (i.e., *re*) face of the rotating vinyl group.

Examination of models indicates that while a 120° rotation suffices to bring the vinyl group into position below C-8 via the anti-CW pathway, a 240° rotation is required in the syn-CCW alternative. If the principle of least motion is considered relevant to an enzyme-catalyzed process such as this, the pathway involving initial anti-S_N' cyclization[23] may be the more likely, in which case the stereospecificity would be in accord with that found recently in the biosynthesis of rosenonolactone,[24] pleuromutilin,[25] and sandaracopimaradiene.[26]

Acknowledgment. We thank Professor Charles A. West, Department of Chemistry, University of California, Los Angeles, for providing the enzyme lyophilisate and for valuable advice on the enzymatic experiments. This research was supported in part by Grant GM-13956 from the National Institutes of Health.

(15) For example, see: (a) P. J. Wagner, *Acc. Chem. Res.*, **4**, 168 (1971); (b) F. D. Lewis, R. W. Johnson, and D. E. Johnson, *J. Am. Chem. Soc.*, **96**, 6090 (1974).

(16) Hanson and co-workers have previously shown that tritium from (5*S*)-mevalonic-*5-t* acid is found in the 14β position of kaurene biosynthesized with an enzyme preparation from *G. fujikuroi*. Thus, the stereochemistry of kaurene biosynthesis at this position is the same in *G. fujikuroi* and *M. macrocarpus*. See: R. Evans, J. R. Hanson, and L. J. Mulheirn, *J. Chem. Soc., Perkin Trans. 1*, 753 (1973).

(17) We are grateful to Dr. Raymond Zelnik, Department of Chemistry, Institute Butantan, São Paulo, Brazil, for supplying the copal resin from which copalic acid, as its methyl ester, was isolated: T. Nakano and C. Djerassi, *J. Org. Chem.*, **26**, 167 (1961); R. M. Coates, P. L. Cavender, and K. A. Drengler, unpublished results.

(18) (i) Bromine addition (Br_2, CH_2Cl_2, 3 equiv of C_5H_5N, 0 °C, 12 h); (ii) ester reduction (AlH_3, ether, -5 °C); (iii) dehydrobromination (KOH, 15:1 C_2H_5OH/H_2O, reflux 4.5 h).

(19) The C-17 vinyl proton appearing at higher field in the NMR spectra of related labd-13(17)-ene derivatives has been assigned the anti stereochemistry.[20] This assignment has been confirmed in our laboratory by analysis of the cyclopropane protons in the NMR spectrum of *ent*-8β,14β-methanopodocarpan-13α-ol-*18-d* prepared from copalol-*17-d*: K. A. Drengler, P. L. Cavender, and R. M. Coates, unpublished results.

(20) P. K. Grant and R. T. Weaver, *Tetrahedron*, **30**, 2385 (1974); R. A. Bell, M. B. Gravestock, and V. Y. Taguchi, *Can. J. Chem.*, **53**, 2869 (1975); P. Sundararaman and W. Herz, *J. Org. Chem.*, **42**, 806 (1977).

(21) The exo stereoselectivity of exchange is similar to that reported for methyl gibberate and bicyclo[2.2.1]heptan-2-one: see ref 16 and G. A. Abad, S. P. Jindal, and T. T. Tidwell, *J. Am. Chem. Soc.*, **95**, 6326 (1973).

(22) W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

(23) For recent reviews, see: (a) D. E. Cane, *Tetrahedron*, **36**, 1109 (1980); (b) K. H. Overton, *Chem. Soc. Rev.*, **8**, 447 (1979).

(24) D. E. Cane and P. P. N. Murthy, *J. Am. Chem. Soc.*, **99**, 8327 (1977).

(25) D. Arigoni and H. Hasler, unpublished results; H. Hasler, Ph.D. Thesis, ETH, Zürich, 1979.

(26) R. M. Coates and K. A. Drengler, *J. Chem. Soc., Chem. Commun.*, in press.

(27) Biomedical Sciences Research Fellow, 1974-1975; Dow Chemical Corporation Fellow, 1975-1976.

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Nature of a Trimethylenemethane-Palladium Complex

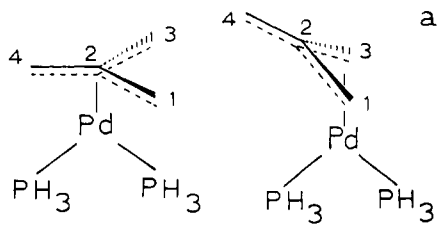
Sir:

Delving into the structure and reactivity of trimethylenemethane (TMM) represents a continuing challenge.[1] Equally fascinating is the chemistry of the metal complexes of such reactive intermediates. The iron tricarbonyl complex of TMM has been shown

(1) For some recent studies, see: Platz, M. S.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 2358. Duncan, C. D.; Corwin, L. R.; Davis, J. H.; Berson, J. A. *Ibid.* **1980**, *102*, 2350, and references cited therein. For a review, see: Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 446.

0002-7863/80/1502-6359$01.00/0

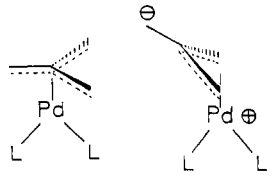
Table I. Charge Distribution in TMM-Pd$(PH_3)_2$



atom		
Pd	+1.158	+1.140
C(1)	−0.364	−0.340
C(2)	+0.202	+0.226
C(3)	−0.364	−0.340
C(4)	−0.589	−0.696
P	+0.448	+0.441

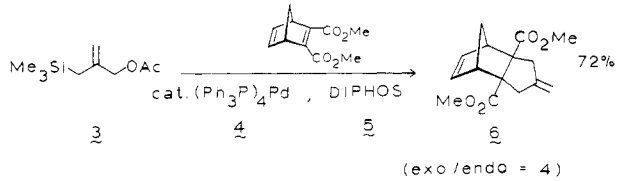
[a] The unsymmetrical structure is predicated on the known geometry of simple π-allylpalladium complexes.

to have C_{3v} symmetry.[2] Preliminary indications also suggest that the nickel complex of TMM shows D_{3h} symmetry for the ligand.[3] We report that, in contrast to these studies, a palladium(0) complex of TMM showed nonequivalence of the methylene carbons, which supports structure **2** rather than **1**.

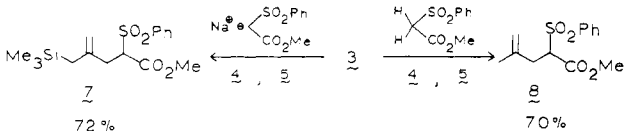


1 2

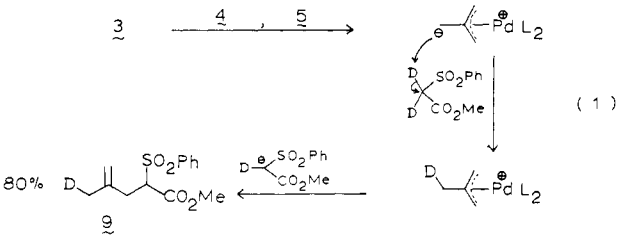
The nucleophilic character of TMM–PdL_2 (L = Ph_3P or L_2 = $Ph_2PCH_2CH_2PPh_2$) generated in situ from **3**[4] is confirmed by the intramolecular competition in cycloaddition with 2,3-di-



carbomethoxynorbornadiene to give the product **6**[5] of exclusive addition to the less electron-rich olefin.[6] Further, reaction of **3** with the preformed sodium salt of methyl benzenesulfonylacetate led to exclusive trapping of the precursor complex to TMM–PdL_2 to give **7** whereas use of methyl benzenesulfonylacetate led ex-

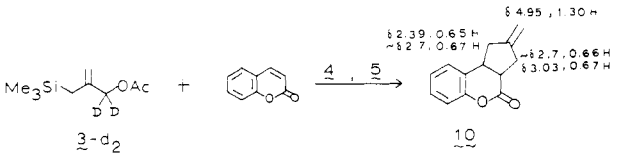


clusively to the desilylated alkylation product **8**. Obviously **7** is not the precursor of **8**. Further, control experiments verify desilylation of starting material does not occur under these conditions. Reaction of deuterated methyl benzenesulfonylacetate followed by washing out of any exchangeable deuterons led to the monodeuterated product **9** [mass spectrum (MS) 91% d_1; ^1H NMR δ 1.66 (br s, ~2.2 H); H decoupled ^{13}C NMR δ 21.89 (t, J = 19.3 Hz)]. These observations require TMM–PdL_2 to be a

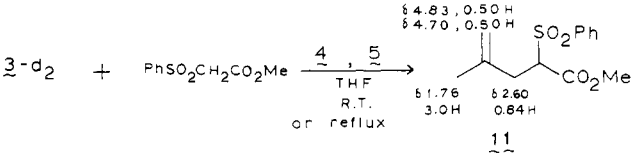


precursor in the alkylation reaction to give **8** and **9** as well as in the cycloaddition reaction. Fenske–Hall calculations on TMM–$Pd(PH_3)_2$ (see Table I) indicate negative charge on carbon,[7] further evidence for the intermediacy of a nucleophilic/basic TMM–PdL_2 complex in these reactions.

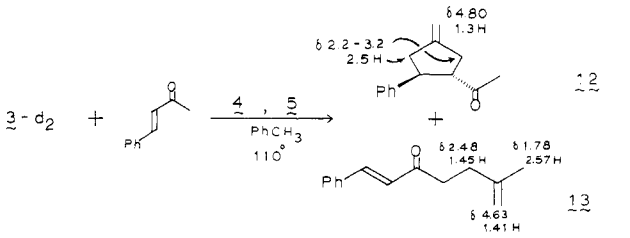
The reactions of the dideuterated derivative **3**-d_2[8] proved most incisive. Cycloaddition of **3**-d_2 (MS 91.4% d_2, 3.3% d_1) to coumarin produced the cycloadduct **10** (MS 89.8% d_2, 5.9% d_1), which



showed full scrambling of the deuterium label to all three methylene carbons of TMM–PdL_2 by both ^1H (see **10**) and ^2H [(C_6F_6, 15.4 MHz) δ 4.91 (1.0 D), 2.27–2.91 (2.0 D)] NMR spectroscopy. On the other hand, reaction of **3**-d_2 with methyl benzenesulfonylacetate led only to scrambling of two of the three methylene groups as summarized in **11** [MS 82.1% d_2, 9.1% d_1; ^2H NMR (C_6F_6, 15.4 MHz) δ 4.56 (1.0 D), 2.45 (1.2 D)].



Considering the high acidity of the sulfone ester (pK_a ~14),[9a] we examined the alkylation reaction with a less acidic compound (pK_a ~24),[9b] benzalacetone, which also allowed simultaneous evaluation of the cycloaddition. Cycloadduct **12** (MS 88.6% d_2, 7.1% d_1) showed complete scrambling by both ^1H (see **12**) and



^2H [(C_6F_6, 15.4 MHz) δ 4.88 (1.0 D), 2.4–2.7 (2.3 D)] NMR spectroscopy. In this alkylation reaction, **13** (MS 89.2% d_2, 6.2% d_1) showed complete scrambling by both ^1H (see **13**) and ^2H [(C_6F_6, 15.4 MHz) δ 4.62 (1.0 D), 2.23 (1.0 D), 1.74 (1.1 D)] NMR spectroscopy.

(2) Ehrlich, K.; Emerson, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 2464. Churchill, M. R.; Gold, K. *Inorg. Chem.* **1969**, *8*, 401. Almenningen, A.; Haaland, A.; Wahl, K. *Acta Chem. Scand.* **1969**, *23*, 1145.

(3) Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett.* **1978**, 4823.

(4) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429, 6423.

(5) All compounds have been characterized by spectral means. New compounds have satisfactory elemental composition.

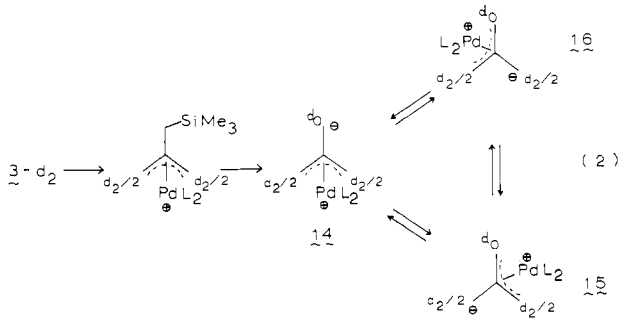
(6) Cf.: Binger, P.; Schuchardt, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 249. Binger, P.; Cetinkaya, M.; Doyle, M. J.; Germer, A.; Schuchardt, U. *Fundam. Res. Homogeneous Catal., Proc. Int. Workshop* **1979**, *3*, 271. Balavoine, G.; Eskenazi, C.; Guillemot, M. *J. Chem. Soc., Chem. Commun.* **1979**, 1109.

(7) These calculations were performed by Fenske, R. F.; Gordon, D. of this department. Cf.: Fenske, R. F. *Prog. Inorg. Chem.* **1976**, *21*, 179.

(8) Prepared by reduction of ethyl 2-(trimethylsilyl) methylacrylate with LAD followed by acetylation. The acrylate was prepared from ethyl 3-(trimethylsilyl) propanoate (Sommers, L. H.; Marans, N. S. *J. Am. Chem. Soc.* **1950**, *72*, 1935) by (i) LDA/THF/−78 °C then $(HCHO)_n$, (ii) CH_3SO_2Cl $(C_2H_5)_3N$/ether/0 °C, and (iii) DBU/ether/room temperature. For an alternative preparation, see: Hosomi, A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, 951.

(9) Extrapolated from the data of Bordwell: (a) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Mathwes, W. S. *J. Org. Chem.* **1977**, *42*, 326. (b) Bordwell, F. G.; Cornforth, F. J. *Ibid.* **1978**, *43*, 1763.

The above results are consistent with TMM-PdL_2 being unsymmetrical as represented by **2** and in eq 2, in direct contradistinction to the case of iron. With a very reactive trap, such



as the highly acidic sulfone ester, the kinetically produced complex **14** protonates faster than it isomerizes. With a less acidic trap, such as benzalacetone, **14** lives longer and allows a palladium migration. A 1,2-migration to **15** and/or **16** effectively scrambles all three methylene groups. α,β-Unsaturated carbonyl compounds represent kinetically slow traps; thus, equilibration overwhelms cycloaddition. Such experimental observations supported by calculations indicate the nucleophilic character of all the methylene carbons of **2** and rationalize the total failure of simple alkyl-substituted olefins (even strained ones) as well as electron-rich olefins to react with TMM-PdL_2.[10] It is noteworthy that although palladium can easily adopt a coordinatively saturated configuration in such complexes it prefers to exist as a η^3 16e species. This study suggests caution must be exercised in the interpretations regarding the structure of other TMM-metal complexes and that the case of iron cannot be simply extrapolated to other metals.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs. Our appreciation to Professor R. F. Fenske and D. Gordon of this department for the calculations is warmly acknowledged. We also thank Mathey-Bishop and Engelhardt Industries for a supply of palladium chloride.

(10) However, reaction of methylenecyclopropanes and olefins catalyzed by palladium is reported to go through TMM complexes (see ref 6). Unfortunately, the available data does not distinguish between a direct cooligomerization reaction (cf. ref 3 and Noyori, R.; Ishigami, T.; Hayashi, N.; Takaya, H. *J. Am. Chem. Soc.* **1973**, *95*, 1674) and reaction through TMM.

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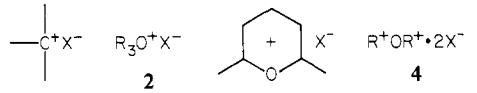
Preparation and Characterization of Novel Dication Ether Salts: $Ar^+OAr^+ \cdot 2CF_3SO_3^-$

Sir:

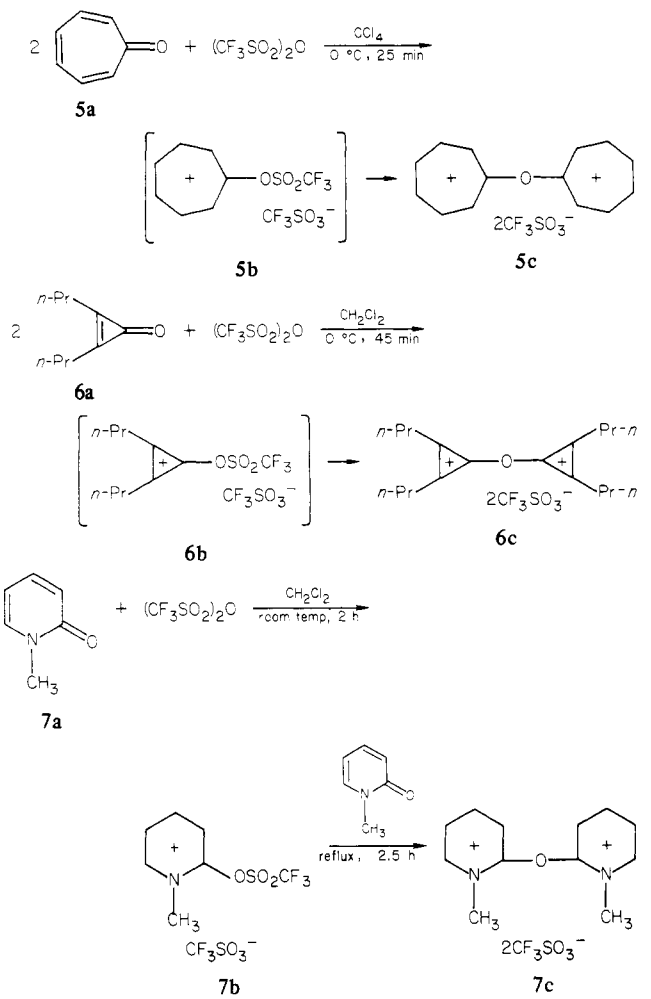
Carbocations (**1**) are among the most common and extensively investigated reactive intermediates.[1] Besides direct spectral observation,[2] generally in superacid media, numerous carbocations



1 2 3 4

have been isolated as stable crystalline salts.[3] Similarly, oxonium (**2**) as well as pyrylium (**3**) ions are well-established organic species.[4] In contrast, carbocations linked by an oxygen, namely, dictation ethers (**4**), are to date unknown. Hence, in this communication, we report the serendipitous preparation of such novel dication ether salts in good yield by a single-step reaction.

Scheme I



Addition of 6.0 mmol of pure $(CF_3SO_2)_2O$ to a magnetically stirred solution of 10 mmol of tropone in 20 mL of anhydrous CCl_4 under an Ar atmosphere at 0 °C results in a colorless crystalline precipitate. Filtration under rigorously anhydrous conditions and recrystallization from anhydrous CH_3CN and ether gave 97% of **5c**. Similarly, 4 mmol of cyclopropenone **6a** and 2 mmol of $(CF_3SO_2)_2O$ in CH_2Cl_2 gave **6c** which could only be characterized in solution. There is little doubt that these reactions proceed through the intermediacy of the respective monocations **5b** and **6b** as shown in Scheme I, but in no case were these intermediates isolable, even with inverse addition to a large excess of anhydride. In contrast, addition of 20 mmol of *N*-methyl-2-pyridone in 15 mL of dry CH_2Cl_2 to 20 mmol of anhydride in 15 mL of dry CH_2Cl_2 resulted, after 2 h at room temperature and subsequent addition of 20 mL of anhydrous ether, in 6.1 g (77%) of crude monocation **7b**. Recrystallization from anhydrous CH_2Cl_2/ether gave pure **7b**. Subsequent reaction of monocation **7b** with an additional equivalent of pyridone **7a** in refluxing CH_2Cl_2 gave after 2.5 h 74% of dication **7c**.

Compounds **5c**-**7c** as well as **7b** were characterized by chemical and spectral means as summarized in Table I. In particular, all dications as well as monocation **7b** are extremely hygroscopic and yield upon exposure to moisture either the expected respective hydroxy cations **5d**-**7d** and/or the starting ketone, depending upon the exact reaction conditions. The identity of the hydrolysis

(1) Olah, G. A.; Schleyer, P. v. R., Eds. "Carbonium Ions", Wiley-Interscience: NY, 1968-1976; Vol. I-V.
(2) Olah, G. A.; Surya Prakash, G. K.; Sommer, J. *Science (Washington, D.C.)* **1979**, *206*, 13-20, and references therein.
(3) Sundaralingam, M.; Chwang, A. K. In "Carbonium Ions"; Olah, G. A.; Schleyer, P. v. R., Eds.; Wiley-Interscience: NY, 1976; Vol. V, pp 2427-2476.
(4) Perst, H. In "Carbonium Ions"; Olah, G. A.; Schleyer, P. v. R., Eds.; Wiley-Interscience: NY, 1976; pp 1961-2047.

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