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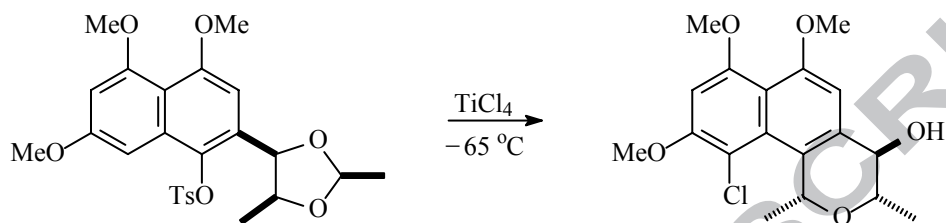
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A novel titanium tetrachloride-induced rearrangement of an enantiopure 4-naphthyldioxolane. The possible role of titanium in the umpolung of tosyloxy and chlorine

Robin G. F. Giles* and Joshua D. McManus



Low temperature rearrangement of a naphthyldioxolane with titanium(IV) chloride affords an angular naphthopyran in which a tosyloxy group is lost from one of the naphthalenic aromatic rings and chlorine is gained with complete regioselectivity by the other. The mechanism of this transformation is of interest.

A novel titanium tetrachloride-induced rearrangement of an enantiopure 4-naphthyldioxolane. The possible role of titanium in the umpolung of tosyloxy and chlorine

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Abstract— The rearrangement of (2'*S*,4'*R*,5'*S*)-2-(2',5'-dimethyl-1',3'-dioxolan-4'-yl)-4,5,7-trimethoxy-naphthalen-1-yl 4"-methylbenzenesulfonate with titanium(IV) chloride affords (1*R*,3*S*,4*R*)-10-chloro-6,7,9-trimethoxy-1,3-dimethyl-3,4-dihydro-4-hydroxynaphtho[1,2-*c*]pyran in good yield. This transformation is characterized by two unusual aromatic substitution reactions in that, in one, tosyloxy is lost and, in the other, aromatic chlorination occurs with titanium(IV) chloride as the source of chlorine.

We report on the rearrangement of the enantiopure 4-naphthyldioxolane **1** using titanium tetrachloride at $-65\text{ }^{\circ}\text{C}$ to provide the naphtho[1,2-*c*]pyran **2**, a transformation involving, *prima facie*, two remarkable electrophilic aromatic substitution reactions. These are an *ipso* electrophilic substitution reaction in which the electrophile departing from one of the aromatic rings is the tosyloxonium ion (TsO^+) and, furthermore, chlorination of the alternative, highly electron-rich aromatic ring occurs with chloride from titanium tetrachloride. We propose a mechanism in which the reagent, titanium tetrachloride, facilitates the complementary umpolung of chlorine and tosyloxy. The yield for this multistep process is 42%, or 65% based on consumed dioxolane **1** and recovered diol **3**.

Suggest Figure showing structures **1**, **2** and **3** be placed here.

The structure, including stereochemistry, of the product naphthopyran **2** follows unambiguously from high-resolution mass spectroscopic, nuclear magnetic resonance and chemical data that will be reported in a subsequent full paper, together with the ready synthesis of the enantiopure dioxolane **1** and details of its transformation into the product **2**. In particular, the aromatic region of the ^1H NMR spectrum shows two one-proton singlets while strongly supportive evidence is provided by entirely consistent correlations in a NOESY spectrum.

In view of the unusual nature of the conversion of dioxolane **1** into naphthopyran **2**, in which two molar equivalents¹ of titanium tetrachloride were used, a possible mechanism is illustrated in Scheme 1. The stereochemistry at C-4 and C-5 in dioxolane **1** is transferred unaltered² to C-4 and C-3, respectively, in the naphthopyran **2**, although it is premature to speculate on the factors controlling the orientation of the product C-1 methyl group. While initial coordination of titanium tetrachloride can occur to either O-1 or O-3 of the dioxolane ring¹ only the latter, giving the preliminary intermediate **4**, leads to an allowed *6-enolendo-endo-trig*³ ring-closure.¹ Consequent cleavage of the C-2/O-3 dioxolane bond and coordination of titanium to both oxygens would require the conformation depicted at the *vicinal* carbons in the derived oxonium ion **5**.

Intramolecular electrophilic aromatic substitution by this oxonium ion could occur either *ortho*- or *para*- to the activating methoxy substituent and the former option would require only the simple loss of a proton to form the corresponding linear naphthopyran. The well-known preference,⁴ however, for naphthalenes to undergo -, rather than -, electrophilic substitution, particularly at low temperatures, leads exclusively, in this case, to *ipso* substitution to afford the -complex **6**.

The simplest mechanism for the transformation of this -complex **6** into the product **2** would be through regioselective nucleophilic attack by chloride at C-10 of the alternative resonance contributor **7** of this complex with the loss of tosylate as shown in Scheme 1. This suggestion, however, raises several questions including, first, why chloride attacks with complete regioselectivity at C-10 rather than also at C-8 (through the third related -complex of **6**) and most particularly at C-5 of the -complex **6**, to afford the 5-chloro-isomer of product **2**. It would reasonably be assumed that, of these three related resonance contributors to the -complex, **6**, giving the 5-chloro-isomer of product **2**, would be the preferred contributor as it does not involve disruption of the aromaticity of the second aromatic ring⁴ as do both of the other resonance contributors, while C-10 is likely to be the most crowded site for nucleophilic attack. Nonetheless it is recognized that the alternative resonance contributors such as **7** are highly conjugated. Second, chloride would be attacking an electron-rich naphthalene, albeit as the derived -complex.

On the other hand, C-10 would be the predicted site for electrophilic chlorination of the naphthalenic aromatic system of the naphtho[1,2-*c*]pyran **8**,^{4,5} particularly at low temperatures, to afford the observed product **2**. In an alternative mechanism the negatively charged titanium in -complex **6** then completes the electrophilic substitution by facilitating the removal of tosyloxy from the ring-system, as shown in **6**, to yield the angular naphthopyran **8**. Also, the two *meta*-disposed methoxy groups on the highly electron-rich terminal aromatic ring combine to achieve electrophilic aromatic substitution of this ring by bonding to one of the chlorine atoms on titanium, as shown in structure **8**, and the electron pair attaching this chlorine to titanium then transfers to the metal. Tosylate can also leave this intermediate complex **8** to furnish -complex **9**. Loss of a proton from **9** and hydrolytic work-up removes the coordinating capacity of titanium and the pyran half-chair undergoes conformational inversion⁶ in order to allow all three substituents on the heterocyclic ring to assume the (pseudo)equatorial orientations observed in the product **2**.

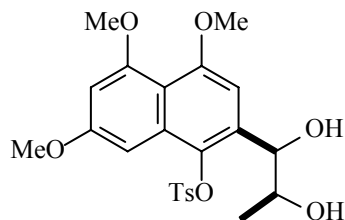
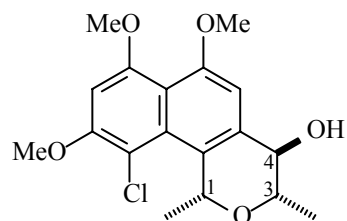
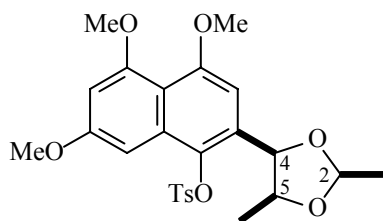
Suggest Scheme 1 be placed here. If more convenient, Scheme 1 could be placed anywhere in the third paragraph where it is discussed.

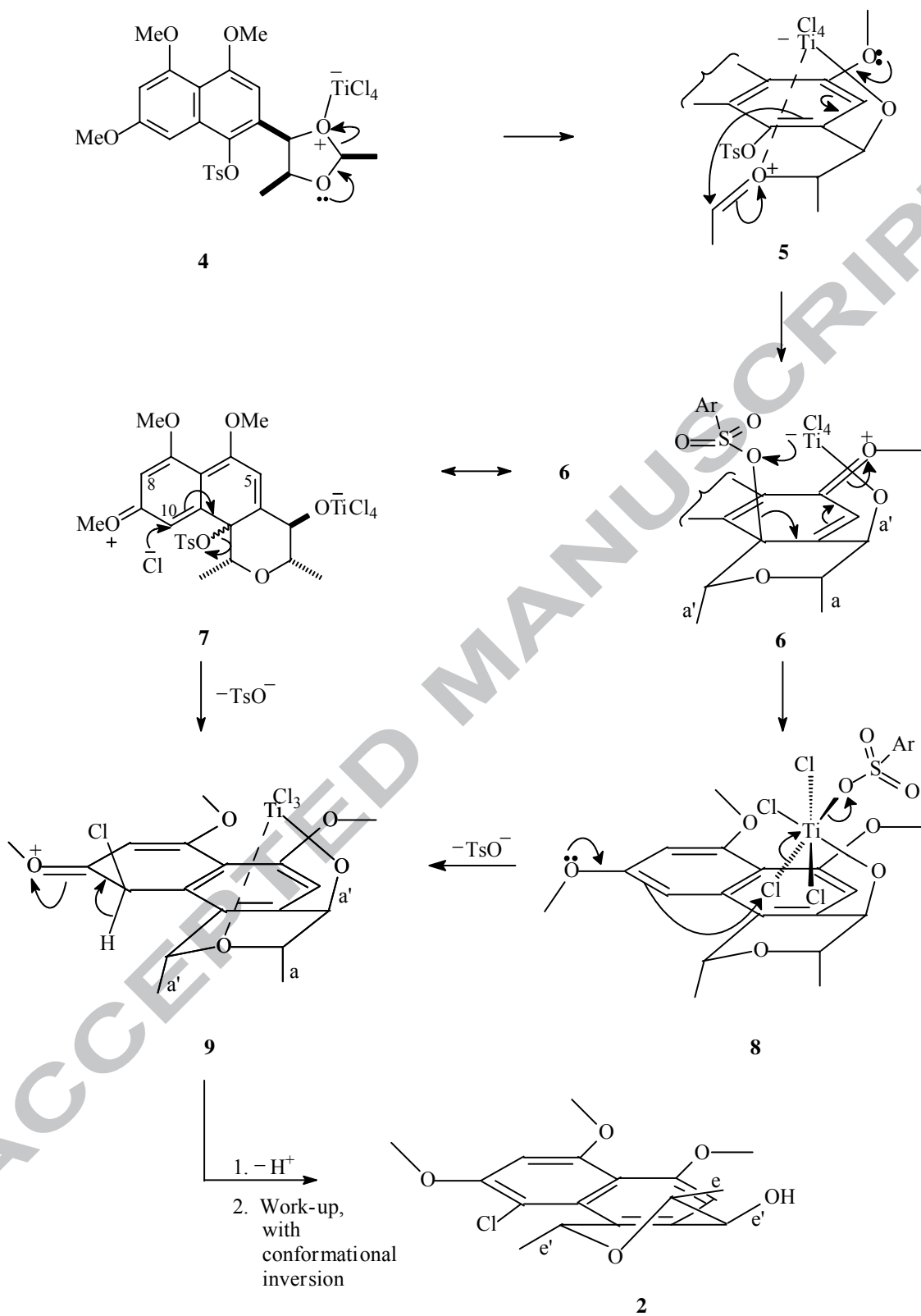
We have previously published two papers^{7,8} reporting several examples of the low-temperature, titanium tetrachloride-induced isomerisations of naphthyldioxolanes into angular naphtho[1,2-*c*]pyrans as the sole products. These examples were very different, however, from the present example since in the first⁷ the -position *ortho*- to the dioxolane in each case was unsubstituted, thereby allowing unfettered -substitution. In

the second paper⁸ this -position was occupied by a bromine atom that prevented, until it was removed, the high-yield formation of angular products.

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Scheme 1