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STEREOCONTROLLED SYNTHESIS OF SUBSTITUTED TETRAHYDROPYRANS FROM 1,3-DIOXAN-4-ONES

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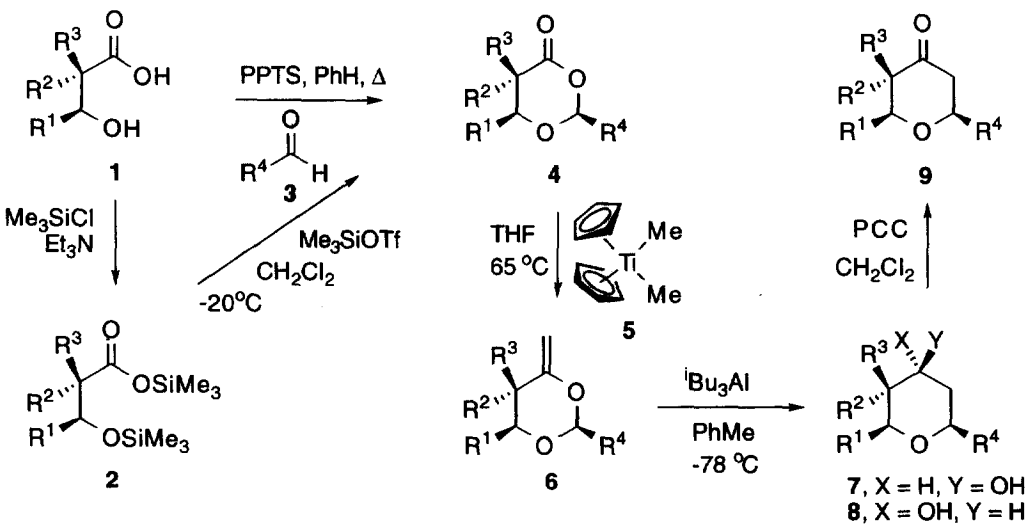
Abstract: Conversion of aldehydes to 1,3-dioxan-4-ones, followed by methylenation with dimethyl titanocene gave the corresponding vinyl acetals which could undergo a stereocontrolled aluminum-mediated rearrangement to afford substituted tetrahydropyrans.

The common occurence of tetrahydropyrans in a wide variety of bioactive molecules, such as polyether antibiotics, marine toxins, lignans, pheromones and C-glycosides, has led to many synthetic approaches for these oxacycles.[1] Although the most common methods rely on intramolecular C-O bond formation or the manipulation of other O-heterocycles, several strategies based on intramolecular reactions of oxocarbenium ions have also been reported.[2] We recently introduced[3] a three-step stereocontrolled approach to substituted tetrahydrofurans involving a titanium-mediated carbonyl olefination followed by an aluminum-promoted rearrangement. We report herein an extension of this method for the synthesis of tetrahydropyrans (Scheme 1).

Scheme 1



The required intermediates for this purpose, i.e. the 1,3-dioxan-4-ones[4] (**4**) were easily prepared by the acetalization of aldehydes (**3**) with β-hydroxyacids (**1**)[4b] or their bis(trimethylsilyl) derivatives (**2**).[4c] The use of chiral β-hydroxyacids[4a,4e] (**1**) in this process gave readily separable diastereomeric acetals (**4**), often in a highly stereocontrolled manner. Methylenation of the carbonyl group of **4** with dimethyl titanocene (**5**)[5] at 65 °C afforded the vinyl acetals (**6**) in good yields. Reaction of **6** with 2 equiv of triisobutylaluminum at -78 °C resulted in the transposition of an O-atom with a C-atom on the ring. In fact, the products of this reaction were the epimeric alcohols **7** and **8**, presumably formed via a concomitant Al-mediated reduction. The relative stereochemistry among C_2 vs C_6 was determined upon oxidation of **7** and **8** to the corresponding ketone derivatives (**9**). Several examples of this concise route to tetrahydropyrans are given in Table 1.

Table 1. Synthesis of tetrahydropyrans from 1,3-dioxan-4-ones (**4**).

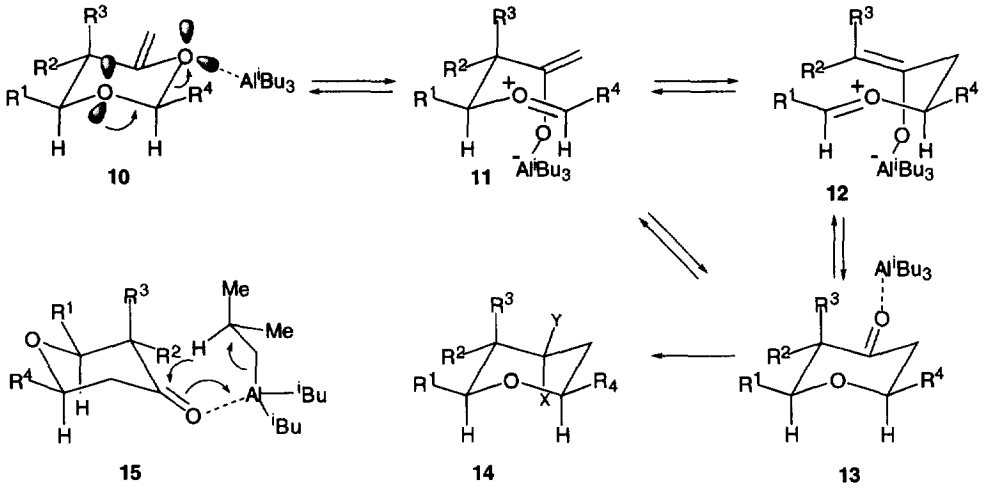
Compd	R^1	R^2	R^3	R^4	Vinyl acetal (**6**)[d,e]	Alcohol[e,f] (**7**:**8**)	Ketone (**9**)[e,g,h]
4a[a]	H	Me	Me	Ph	72%	91% (1:1)	96%
4b[a]	Me	H	H	^{t}Bu	88%	81% (1:1.5)	
4c[b]	Me	H	H	$(CH_2)_2Ph$	86%	96%	98% (86%cis)
4d[b]	Me	H	H	$(CH_2)_9Me$	80%	93%	95% (88%cis)
4e[a]	Me	H	H	Ph	70%	90%	93% (93%cis)
4f[b]	H	Ph	H	^{i}Pr	67%	88% (1:8)	92% (>99%cis)
4g[b]	H	H	Ph	^{i}Pr	65%	90% (1:0)	
4h[c]	Me	$PhCH_2$	H	^{t}Bu	75%	92% (1:8)	

[a]Prepared from **2** and **3**.[4c] [b]Prepared from **1** and **3**.[4b] [c]Prepared by the alkylation of **4b** with LDA at -78 °C and benzyl bromide.[6] [d]Vinyl acetals were prepared by the reaction of **4** with dimethyltitanocene at 65 °C in THF.[5] [e]Yields were determined followed isolation by distillation or chromatography and were not optimized. [f]Obtained by the reaction of the vinyl acetal with 2 equiv. of $^iBu_3Al$ in toluene at -78 °C. [g]Obtained by oxidation of the alcohol with PCC in CH_2Cl_2. [h]Ratios of the relative stereochemistry at C_2 and C_6 were determined with NMR and are indicated in parentheses.

An additional attractive feature of this approach is that the alkylation of 1,3-dioxan-4-ones (**4**) can proceed with a high degree of stereocontrol.[6] Indeed treatment of **4b** with LDA followed by reaction with benzyl bromide gave **4h** as a single product. Methylenation to **6h** and rearrangement gave **8h**[7] as the major product.

Mechanistically, the aluminum-mediated [1,3]-sigmatropic rearrangement of **6** is a stepwise transformation, presumably initiated upon the coordination of the aluminum with the enolic O-atom[8] (Scheme 2). Subsequent cleavage of the adjacent C-O bond, with the possible assistance of the antiperiplanar lone electron pair of the other O-atom (**10**), results in the stereospecific generation of the oxocarbenium enolate (**11**), which can be cyclized directly to the oxacycle (**13**). Alternatively, a rare and rather unlikely oxonia-Cope rearrangement[2f,2g,9] of **11** would give **12**, which could cyclize to the same product **13**. Interestingly, when $R^4 \neq H$ the stereochemical information included in **11** is not lost upon its rearrangement to **12** and is retained in the cyclized product (**13**).

Scheme 2



In contrast to the synthesis of tetrahydrofurans,[3] which requires higher temperatures, the aluminum-mediated rearrangement of **6** takes place readily at -78 °C. This difference may be due to the fact that the conversion of **11** (or **12**) to **13** is a 6-(enolendo)-endo-trig cyclization which is more facile than the corresponding 5-(enolendo)-endo-trig process.[10]

The stereochemical outcome of the final step, i.e. the aluminum-mediated carbonyl reduction to form **14**, depends heavily on the substitution pattern. The observed selectivities in this process indicate an *intramolecular* delivery of a hydride from the complexed $^iBu_3Al$ rather than the intramolecular attack by another molecule.[11] As shown in **15**, when R^3=H the reaction can proceed with *steric approach control*[12] favoring the formation of the axial alcohol (**8**). Indeed, this is the major product observed in these cases (e.g. **8f**,[7] **8h**[7]).

In summary, we have found that carbonyl olefination of 1,3-dioxan-4-ones followed by aluminum-mediated rearrangement results in the stereoselective formation of tetrahydropyran derivatives. An attractive feature of this expedient and convergent method for the preparation of functionalized oxacycles is the facile and stereoselective preparation of the starting 1,3-dioxo-heterocycles from carbonyl compounds and hydroxyacids.

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