Organic Synthesis utilizing Beckmann Fragmentation:[1] Highly Stereoselective C–C Bond Formation in the Reaction of 2,3-Isopropylidenedioxycyclohexanone Oxime Esters with Organoaluminium Reagents

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Highly stereoselective C–C bond formation occurred in the reaction of 2,3-isopropylidenedioxycyclohexanone oxime esters with organoaluminium reagents and the reaction was applied to the syntheses of (±)-*endo*-brevicomin and the synthetic intermediate of (±)-juvenile hormone.

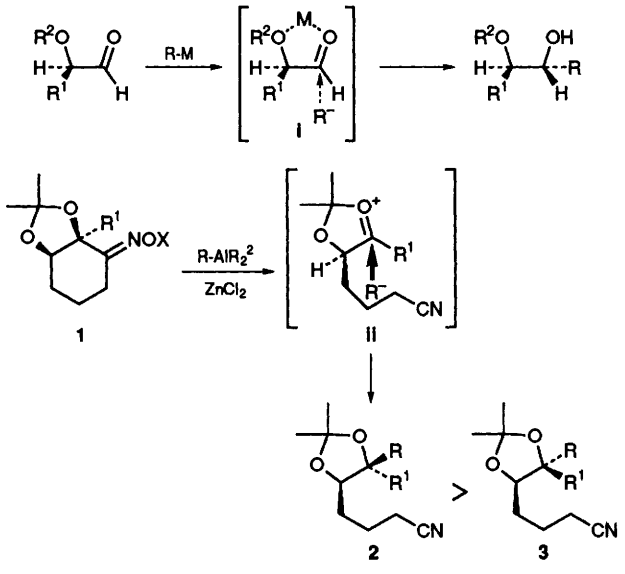
The high stereoselectivity observed in the chelation-controlled nucleophilic addition of organometallic reagents (RM) to chiral α-alkoxy carbonyl compounds has been explained by assuming a rigid five-membered ring intermediates such as **i** (Scheme 1)[2]. This seems to suggest that C–C bond formation *via* the intermediate corresponding to **i** would proceed in a highly stereoselective manner. Recently we reported a new C–C bond forming process by the reaction of α-alkoxycycloalkanone oxime acetates with organoaluminium reagents.[1c] As an extension of this work, we applied the reaction to the α,β-isopropylidenedioxycycloalkanone oxime systems **1**, hoping that highly stereoselective C–C bond formation would occur *via* a rigid five-membered ring intermediate **ii**. We now report that the reaction proceeds in a highly stereoselective manner with the opposite orientation to that involving **i** to give **2** selectively; we have applied the method to the syntheses of (±)-*endo*-brevicomin and the synthetic key intermediate of (±)-juvenile hormone.

The acetonide cycloalkanone oxime esters **1** were prepared by esterification of the oximes which were obtained by oximation of the corresponding α,β-isopropylidenedioxycycloalkanones. Table 1 summarizes the results of the reaction

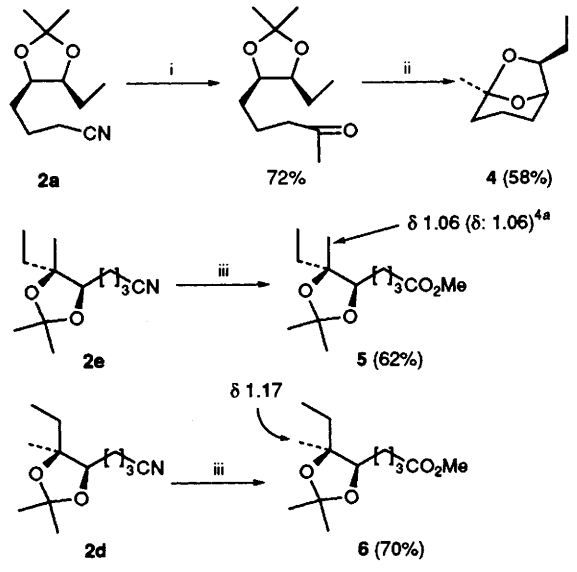
Table 1 Reaction of acetonide oxime esters **1** with organoaluminium reagents[a]

Run	Oxime ester **1**	Reagent	Product **2, 3**	Yield (%)[b]	**2**/**3**[c]
1	**1a** (R^1 = H, X = Ac)	Et_3Al	**a** (R^1 = H, R = Et)	42	10/1
2	**1a**	Me_3Al	**b** (R′ = H, R = Me)	32	10/1
3	**1b** (R^1 = H, X = 2,6-$Cl_2C_6H_3CO$–)	Et_3Al	**a**	82	10/1
4	**1b**	Me_3Al	**b**	83	7/1
5	**1b**	$Bu^nC{\equiv}CAlEt_2$	**c** (R^1 = H, R = $Bu^nC{\equiv}C$)	61	7/1
6	**1c** (R^1 = Me, X = 2,6-$Cl_2C_6H_3CO$–)	Et_3Al	**d** (R^1 = Me, R = Et)	82	7/1
7	**1d** (R^1 = Et, X = 2,6-$Cl_2C_6H_3CO$–)	Me_3Al	**e** (R^1 = Et, R = Me)	80	9/1
8	**1d**	$Bu^nC{\equiv}CAlEt_2$	**f** (R^1 = Et, R = $Bu^nC{\equiv}C$)	65	1.3/1

[a] **1** (0.1 mmol) and $ZnCl_2$ (2 equiv.; 1 mol l^{-1} ethereal solution or $ZnCl_2{\cdot}Et_2O$ complex in CH_2Cl_2 solution) in CH_2Cl_2 (1 ml) were stirred for 10 min at −78 °C and then the organoaluminium reagent (3 equiv.) was added and the resulting mixture stirred at the same temperature. After completion of the reaction (TLC), the resulting mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$ and evaporated. The residue was purified by SiO_2 column chromatography to afford the product (**2** and **3**). [b] Yield of the isolated product, mixture of **2** and **3**. [c] Determined by 500 MHz ^1H NMR spectroscopy.



Scheme 1



Scheme 2 *Reagents and conditions*: i, MeMgI, Et_2O, reflux, then H_2O; ii, AcOH–H_2O (1 : 1), room temp.; iii, 40% aq. KOH–MeOH (1 : 1), reflux, then CH_2N_2

of acetonide oxime esters with organoaluminium reagents. Initially we examined the reaction of the oxime acetate **1a** with Et_3Al in dichloromethane. The reaction proceeded in a low yield (42%) in the presence of zinc chloride to give the desired nitrile compound (10 : 1 mixture of *cis*- and *trans*-isomers, **2a** and **3a**; run 1), whereas the use of only Et_3Al or a combination of Et_3Al and other Lewis acids such as $BF_3{\cdot}Et_2O$, $TiCl_2(OCHMe_2)_2$, $SnCl_4$ and $Me_3SiOSO_2CF_3$ gave poor results. Similar reactivity was observed in the reaction of Me_3Al (run 2). The leaving group (–OAc) was then replaced with a more electron-withdrawing group (2,6-dichlorobenzoyloxy). The yields increased dramatically and a high stereoselectivity was also obtained (runs 3–5). The reaction was applied to the 2-alkyl-2,3-isopropylidenecyclohexanone oxime esters **1c** and **1d** and high selectivity was obtained (runs 6, 7), although the use of hexynyldiethylaluminium resulted in low selectivity (run 8).

The stereochemistry of the products was determined as follows. That of **2a** was determined by converting it to a known compound. Thus, the reaction of pure **2a** with MeMgI followed by acid treatment gave (±)-*endo*-brevicomin **4**,[3] an attraction pheromone of several pine beetle species belonging to the genera *Dendroctonus* and *Dryocetes*. The stereochemistry of the products in runs 4 and 5 was tentatively assigned by assuming the same sense of diastereoselection as observed for **2a**. The stereochemistry of **2d** and **2e** was determined by converting **2e** to the synthetic intermediate **5**[4] of juvenile hormones I and II. Alkaline hydrolysis of **2e** followed by esterification gave compound **5**, whose ^1H NMR data showed good agreement with the reported values;[4a] **2d** was converted to the epimeric product **6** in the same manner (Scheme 2).

As mentioned above, the major products shown in Table 1 were formed by the attack of the reagents from the same side of the alkyl side chain in the transition state. Although the reaction mechanism and stereochemical course have not been ascertained, the results may be rationalized by the counter anion being placed on the opposite side of the alkyl side chain in the oxonium ion intermediate **ii** and the introduced alkyl unit attacking from the same side of the side chain owing to electrostatic repulsion and/or steric hindrance.

In conclusion, highly stereoselective C–C bond formation was attained in the reaction of 2,3-isopropylidenedioxycyclohexanone oxime esters and organoaluminium reagents and a new way to get ω-cyano-1,2-diol compounds selectively is obtained. It is noteworthy that the predominant products are formed by the attack of the nucleophiles from the same side of the alkyl side chain in the intermediate **ii**, whereas the attack of the nucleophiles occurs from the opposite side of the alkyl side chain in the intermediate **i**.

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