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Facial Selectivity in the Nucleophilic Additions of *endo*-Tricyclo[5.2.1.$0^{2,6}$]deca-2(6),8-dien-3-one

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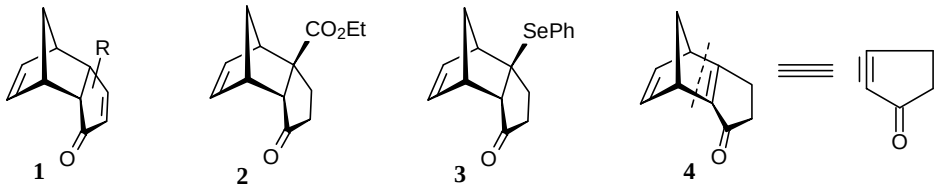
Abstract: Nucleophilic additions to *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-2(6),8-dien-3-one **4** are described. Experimental results show high preference for *exo*-facial attack to the enone moiety of tricyclodecadienone. Steric hindrance is the main kinetically controlling factor in the nucleophilic reaction. The shielding effect and the stabilizing effect of the norbornene double bond favor the *exo*-facial attack also.

Keywords: Stereochemistry, nucleophilic addition.

The *endo*-tricyclo [5.2.1.$0^{2,6}$] decadienone system **1** has been used as a versatile synthon for the synthesis of a great variety of natural products[1]. The availability of both antipodes of **1** in enantiopure form[2], and the ability to undergo [4+2] cycloreversion makes it useful for the enantioselective synthesis of naturally occurring cyclopentanoids with defined stereochemistry and chirality[3].

Starting from the 1,4 reduced Hertz ester **2**, synthesis of the reactive and strained tricyclodecadienone **4** was achieved by oxidative elimination of phenylselenyl compound **3**[4]. Tricyclodecadienone **4** can be considered as a synthetic equivalent of the cyclopentynone whereas the tricyclodecadienone system **1** is a synthetic equivalent of cyclopentadienone,

Scheme 1



Nucleophilic additions to tricyclodecadienone **4** might lead to two stereo isomers *endo*- or *exo*-tricyclic compound (**Scheme 2**). It depends on steric and electronic factors

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as well as the stability of the intermediates or the final products. The main goal of this study is to figure out the factors which determine the stereoselectivity in nucleophilic additions of *endo*-tricyclo [5.2.1.$0^{2,6}$] deca-2(6),8-dien-3-one **4**.

The Michael addtion of a series of nucleophiles to **4** was investigated under protic conditions. As shown in **Scheme 2,** the nucleophile can approach the enone either from the *exo* or the *endo* face.

Scheme 2

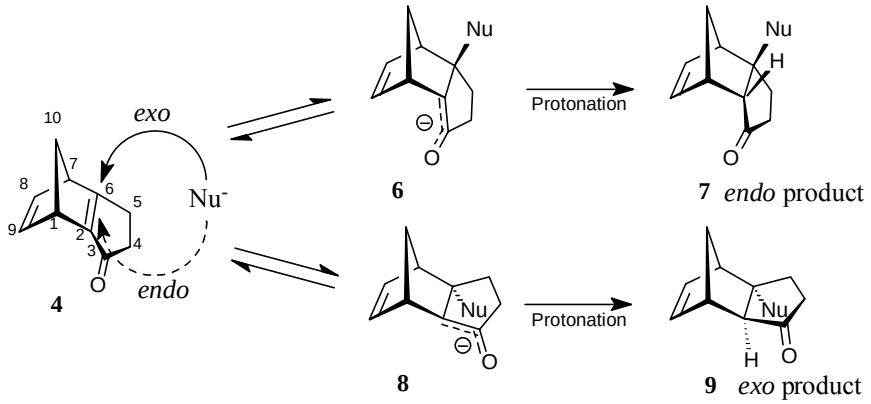


Table 1 Experimental results of nucleophilic addition under protic condition

Compound	Solvent	Base	Nucleophile	Time (hrs)	Product	Yield (%)
4	t-BuOH	NaOH	t-BuO^-	72	**7a** (Nu = HO)	67
4	MeOH	NaOH	MeO^-	0.25	**7b** (Nu = MeO)	99
4	EtOH	NaOH	EtO^-	1	**7c** (Nu = EtO)	97
4	n-BuOH	NaOH	n-BuO^-	2	**7d** (Nu = n-BuO)	65
4	i-PrOH	NaOH	i-PrO^-	6	**7e** (Nu = i-PrO)&7a	35&20
4	MeCN	KCN	CN^-	72	**7f** (Nu = CN)	95
4	MeCN	NaH	$CH(CO_2Et)_2^-$	120	**7g** (Nu = $CH(CO_2Et)_2$)	73

The experimental results clearly showed that the products obtained were exclusively in *endo*-form **7** (**Table 1**). The kinetically controlled product formation is determined by steric and electronic factors of **4**. Sterical hindrance of the methylene bridge is less than the ethylene group therefore nucleophilic attacks from the *exo*-face of the cyclopentenone moiety in **4** is kinetically favored over *endo*-facial addition. Moreover, addition from the *exo*-face may also be favored electronically. The orbital interaction between the olefinic C_8-C_9 bond and the enone π-system may lead to an effective shielding of the *endo*-face of **4** for incoming nucleophiles. The stabilization effect of the olefinic C_8-C_9 bond enhances initial bond formation while the nucleophiles attack from the *exo*-face.

Michael additions under aprotic conditions were also investigated using lithium dialkylcuprates as the nucleophilic reagents in diethyl ether. The results are shown in the following **Table 2**.

The results imply that the addition of lithium dialkylcuprates under aprotic condition also primarily takes place by an *exo*-facial attack, but not uniquely. When the alkyl was changed from methyl to butyl in dialkylcuprates, the steroselectivity was enhanced in some degree.

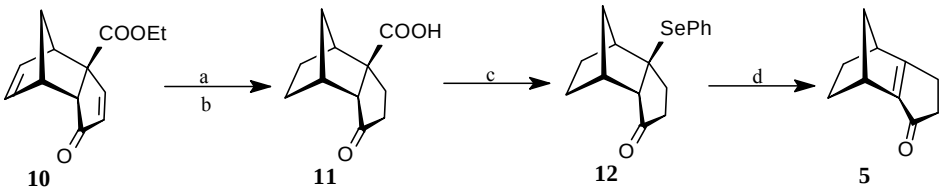
Table 2 Experimental results of nucleophilic addition under aprotic condition

Compound	Nucleophile	Condition	Poduct	Yield %
4	Me_2CuLi	15min/-78°C	**7 h & 9 h**	82 (10:1)
4	$(n\text{-}Bu)_2CuLi$	15min/-78°C	**7i & 9i**	92 (19:1)

But even with the bulky nucleophile the *exo*-product was still observed. Thus, we can make the conclusion that steric effect is the main controlling factor in this nucleophilic reaction. However some electronic effect must be involved in the formation of the *exo*-products. The mechanism of the *endo* addition of lithium dialkylcuprates is suggested that the dialkylcuprates may coordinate with the enone moiety and the olefinic C_8-C_9 bond while the attack occurs from the *endo*-face of substrate **4** to produce the *exo*-product.

The special nature of the cuprate addition reaction involving formation of complex with the C_8-C_9 olefinic bond can be verified by investigation of the facial selectivity of lithium dialkyl cuprate addition reactions to tricyclodecenone **5**, which lacks the C_8-C_9 double bond. The synthesis of **5** is described in **Scheme 3**.

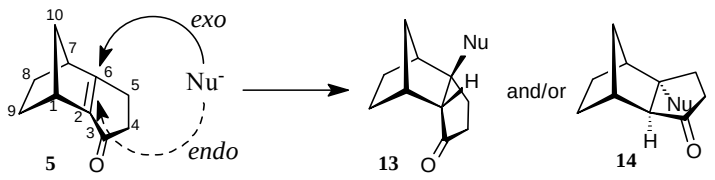
Scheme 3



a) H_2, Pd/C, 95%; b) 0.2N NaOH, H^+, 97%; c) $(CO)Cl_2$,  , $(PhSe)_2/h\nu$, 90%; d) $NaIO_4$/MeOH, 81%

Starting with Hertz ester **10**, palladium catalyzed reduction followed by hydrolysis gave the completely reduced tricyclodecanone acid **11**. After decarboxylation under Barton conditions[5] with diphenyldiselenide as trapping agent, phenylselenyl-*endo*-tricyclodecanone **12** was obtained in good yield. Oxidative elimination of the phenylselenyl group gives the desired tricyclodecenone **5** in a good yield.

Scheme 4



Michael additions to **5** were studied under aprotic and protic conditions using two lithium dialkylcuprates and sodium hydroxide in methanol. The experimental results are collected in **Table 3**.

Table 3 Experimental results of nucleophilic addition to compound **5**

Compound	Nucleophile	Condition	Product	Yield %
5	Me_2CuLi	2hrs/-78°C	**13a** (Nu=Me)	82
5	$(n\text{-}Bu)_2CuLi$	2hrs/-78°C	**13b** (Nu= n-Bu)	85
5	MeOH/NaOH	20hrs/rt	**13c** ((Nu=MeO)	65

As expected the nucleophilic addition to **5** is completely *exo*-facial selective. It should be noted that addition reaction rates to **5** were considerably slower than those to **4**. The complete *exo*-selectivity indicates that the stereoselectivity is fully governed by the steric factor. The difference of reaction rates between substrate **4** and **5** clearly showed the effect of coordination and stabilization of the norbornene C_8-C_9 double bond in **4**.

Conclusion

The nucleopilic addition to the enone moiety of tricyclodecadienone **4** is mainly *exo*-facial attack. The facial selectivity can be explained by steric approach control in a kinetically controlled process. Moreover, an orbital interaction between the norbornene C_8-C_9 bond and the enone system may favor the *exo*-facial approach of the nucleophile. The stabilizing effect of the olefinic C_8-C_9 double bond which assists the initial bond formation promotes the *exo*-facial attack also. The low reactivity of **5** which lacks such olefinic C_8-C_9 bond could be a good evidence of this influence.

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