Pergamon

Tetrahedron Letters 41 (2000) 9803–9807

TETRAHEDRON LETTERS

Asymmetric Mn(III)-based radical synthesis of functionalized 2,3-dihydrofurans

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Received 28 July 2000; accepted 28 September 2000

Abstract

The oxidative radical addition of alkyl acetoacetates to *p*-methoxycinnamoyl oxazolidinones promoted by Mn(III) has been studied. It only gives *trans*-disubstituted 2,3-dihydrofurans, with d.r. ranging from 2:1 to 9:1, depending on the substituent of the chiral auxiliary. After chromatographic separation of the two diastereomers, the oxazolidinone can be removed to afford enantiopure dihydrofuranyl esters in good overall yield.

Keywords: optically active trans-2,3-disubstituted dihydrofurans; radical asymmetric synthesis; oxidative cyclization; manganese(III) acetate.

The tetrahydrofuran ring is a ubiquitous motif which can be found in numerous natural products (e.g. polyether antibiotics, nucleosides, lignans).[1] Clearly, general methods to prepare non-racemic substituted THF are needed in order to address the extraordinary diverse pattern of stereochemistry and substitutions existing in these THF-containing natural products. One such approach could consist of the initial synthesis of functionalized chiral 2,3-dihydrofuran precursors whose functionalities and remaining double bond could be subsequently manipulated.

The $Mn(OAc)_3$-mediated oxidative free radical addition of acetoacetic esters to alkenes represents one such useful synthetic reaction as it cleanly furnishes, in one step, 2,3-dihydrofurans as the sole products (provided that the reaction is performed in the absence of oxygen, in order to prevent the formation of unwanted cyclic peroxides).[2] Furthermore, when using methyl cinnamates as substrates, it has been shown to be totally regio- and diastereoselective, giving a single diastereomer (possessing two esters of markedly different chemical reactivity and two vicinal stereocenters in a *trans* relative relationship) in fair to good yield depending essentially on the nature of Ar (Scheme 1).[3]

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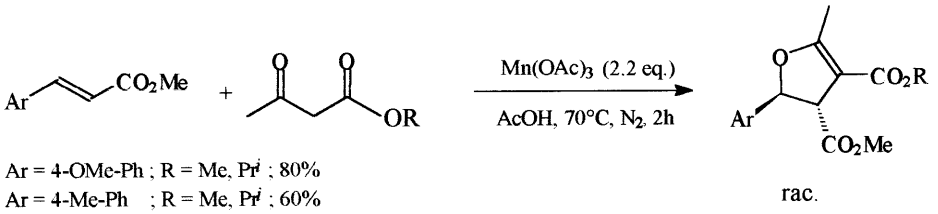
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01729-9

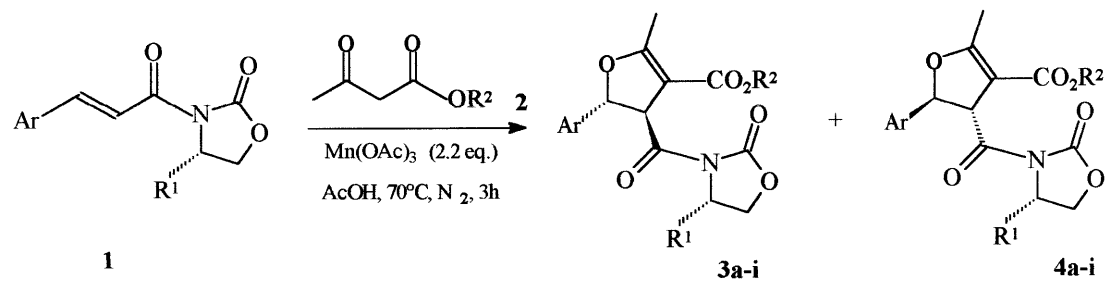


Scheme 1.

Surprisingly, no results could be found in the literature concerning the control of the absolute configuration of these stereocenters in the case of intermolecular additions and very little work has been published on intramolecular versions of this reaction.[4]

We thus endeavoured to study this control by using chiral auxiliaries linked to the cinnamoyl moiety (α selectivity)[5] choosing, in this communication, to evaluate the capability of oxazolidinones as these chiral controllers (despite the fact that, in the only previous case when they were tried in an intramolecular Mn(III)–Cu(II) oxidative cyclization, the substrate failed to react).[4a–c] Indeed, oxazolidinones constitute excellent chiral auxiliaries due to the diversity and ready availability of precursor amino acids (natural and unnatural), their ease of grafting onto the substrate and cleavage from the intermediate product. Moreover, their robustness could enable them to survive the acidic conditions, the elevated temperature and the duration necessary to carry out this reaction. Their usefulness for acyclic diastereoselection in other radical addition reactions is well documented[5] but, in order to obtain significant diastereoselectivities, it is quite often necessary to use them in conjunction with an added Lewis acid to chelate the two carbonyls of the *N*-acyloxazolidinone thereby restricting the number of possible rotamers.[6] Nonetheless, we hoped that Mn salts might somehow exhibit a chelating role thus obviating the need for an extra Lewis acid.

In order to determine which factors control the diastereoselectivity, we decided to react alkyl acetoacetates[7] with *p*-methoxycinnamoyl oxazolidinones,[8] varying the nature of the R^1 substituent on the oxazolidinone and of the R^2 substituent on the ester. Our results are summarized in Scheme 2 and Table 1.[9]



a R^1 = $PhCH_2$, R^2 = Me
b R^1 = $PhCH_2$, R^2 = Pr^i
c R^1 = Pr^i, R^2 = Me
d R^1 = R^2 = Pr^i
e R^1 = Bu^t, R^2 = Me
f R^1 = Bu^t, R^2 = Pr^i
g R^1 = Bu^t, R^2 = 1-Adamantyl
h R^1 = Ph_2CH, R^2 = Me
i R^1 = Ph_2CH, R^2 = Pr^i

Scheme 2.

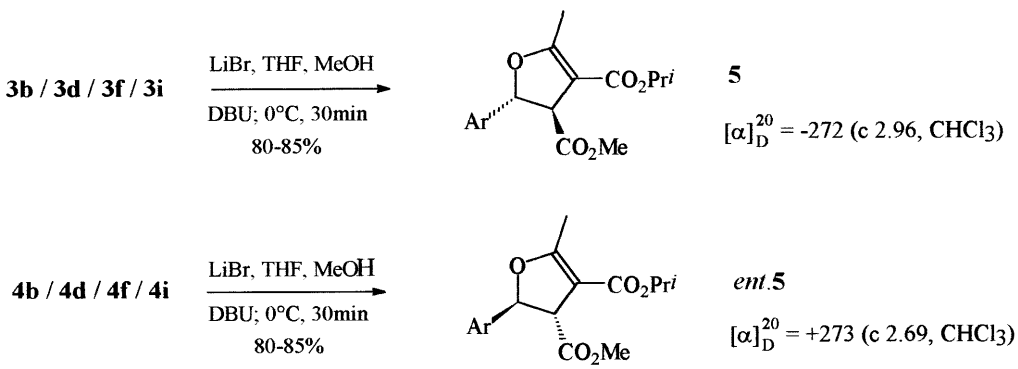
Table 1
Addition of acetoacetic esters **2** on cinnamoyloxazolidinones **1**. Relative ratio of diastereomers **3**:**4**

Entry	**1** (R^1)	**2** (R^2)	**3**:**4**[a]	Yield (%)	Unreacted **1** (%)
1	$PhCH_2$	Me	2:1	80[b]	8
2	$PhCH_2$	Pr^i	2:1	72[c]	9
3	Pr^I	Me	2.7:1	75[b]	5
4	Pr^I	Pr^i	2.7:1	69[c]	15
5	Bu^t	Me	5.3:1	80[b]	10
6	Bu^t	Pr^i	5.3:1	74[c]	10
7	Bu^t	Ad[d]	5.3:1	65[c]	10
8	Ph_2CH	Me	9:1	80[c]	Traces
9	Ph_2CH	Pr^i	9:1	75[c]	5

[a] Determined on the crude product by ^1H and ^{13}C NMR (250 MHz) and GC on an SE30 capillary column.
[b] Purified mixture of non separable **3**+**4**.
[c] Pure isolated **3** and **4**.
[d] Ad = 1-adamantyl.

As can be seen, the regio- and trans diastereoselectivities as well as the overall yield of isolated dihydrofurans are retained on going from an achiral *p*-methoxycinnamate (Scheme 1) to a chiral one. In each case, **3** and **4** are the only products formed in a relative ratio depending exclusively on the R^1 substituent of the oxazolidinone: the d.r. increases (from 2:1 to 9:1) with the bulkiness of R^1 while the R^2 group on the radical precursor plays no part in the discriminative step (compare entries 1/2, 3/4, 5/6/7, 8/9). This is in good accord with a proposed model accounting for the sense of diastereoselection in radical additions using *N*-enoyloxazolidinones and a chelating agent,[6] positioning R^1 in such a way as it will preferentially shield one of the diastereotopic faces of the enoyl moiety.[10]

In all instances where $R^2 = Pr^i$, the two diastereomers **3** and **4** could be readily separated by chromatography and the oxazolidinone removed by methanolysis to give enantiopure **5** and *ent*. **5**, respectively (Scheme 3).[11]

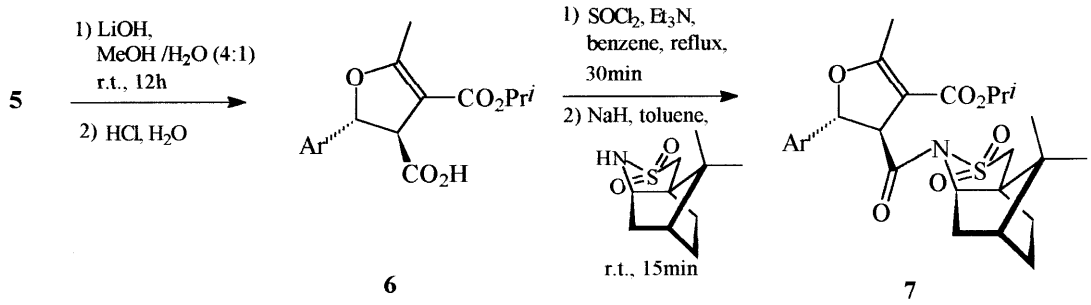


Scheme 3.

Determination of the absolute configuration

As in any of the cases already tested, neither **3** nor **4** could be induced to crystallize, we prepared enantiomerically pure crystalline **7** (75% overall yield) by selective monosaponification

of enantiopure **5** into the monoacid **6**, formation of its acid chloride and in situ reaction with the sodium salt of (–)-10,2-camphorsultam[12] (Scheme 4).



Scheme 4.

An X-ray structure determination of **7** allowed to unambiguously establish the absolute configuration of the stereocenters on the dihydrofuran moiety as being 2*R* and 3*R*. It follows that **5** is (2*R*,3*R*) and *ent*. **5** (2*S*,3*S*) as depicted in Scheme 3.

We have shown for the first time that the intermolecular Mn(III)-mediated oxidative addition of acetoacetic esters to alkenes can afford a high level of stereocontrol like its intramolecular counterpart. The reaction gives rise to enantiopure 2,3-dihydrofuranyl diesters in good overall yield. In order to extend its synthetic scope, the study of other chiral auxiliaries is underway.

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7. Except for commercially available methyl acetoacetate, alkyl acetoacetates **2** were prepared from 2,2,6-trimethyl–4*H*-1,3-dioxin-4-one and the appropriate alcohol in refluxing xylene.

8. Cinnamoyloxazolidinones **1** were obtained by reaction of *p*-methoxycinnamoyl chloride and the lithium salt of oxazolidinones derived from (*S*)-phenylalaninol ($R^1 = PhCH_2$), (*S*)-valinol ($R^1 = Pr^i$), (*S*)-*tert*-leucinol ($R^1 = Bu^t$) and (*R*)-serine methyl ester ($R^1 = Ph_2CH$) in THF.
9. General procedure: *N*-cinnamoyloxazolidinone **1** (1 mmol), alkyl acetoacetate **2** (1 mmol) and $Mn(OAc)_3 \cdot 2H_2O$ (590 mg, 2.2 mmol) in acetic acid (10 mL) were heated at 70°C under nitrogen for 3 h. After cooling, water was added and the mixture extracted with diethyl ether. The organic extracts were washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent afforded the crude product which was purified by flash chromatography (hexane/ether: from 16:1 to 1:1) giving first unreacted **1** then **3** and **4**. All new compounds exhibited spectral (IR, NMR) and analytical characteristics consistent with their structure.
10. It was shown that the reaction of *N*-acetoacetyloxazolidinones with methyl *p*-methoxycinnamate gives two diastereomeric dihydrofurans in lower combined yield (40–45%) and with a poor d.r. (1.5:1), independently of R^1 ($PhCH_2$, Pr^i, Bu^t). This result demonstrates that the diastereoselectivity is essentially substrate-controlled.
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