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The stereoselective addition of titanium(IV) enolates of 1,3-oxazolidin-2-one and 1,3-thiazolidine-2-thione to cyclic *N*-acyliminium ion. The total synthesis of (+)-isoretronecanol

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Abstract—(+)-Isoretronecanol (**1**) has been prepared in four steps and 36% overall yield via the diastereoselective addition of the titanium(IV) enolate derived from *N*-4-chlorobutyryl-1,3-thiazolidine-2-thione (**3**) to *N*-Boc-2-methoxypyrrolidine (**5**), which afforded 2-substituted pyrrolidine **7** in 84% yield (8:1 diastereoisomeric ratio), followed by reductive recovery of the chiral auxiliary and cyclization.

Metallic enolates from chiral *N*-acyl 1,3-oxazolidin-2-ones display a central role in modern synthetic organic chemistry.[1] The progress in the field has been pioneered by Evans et al. who described the efficiency of boron enolates of 1,3-oxazolidin-2-ones in the construction of *syn* aldol products.[2] The utility of titanium(IV) enolates of *N*-acyl 1,3-oxazolidin-2-ones and 1,3-oxazolidine-2-thiones[3] as well as the tin(II) enolates of *N*-acyl 1,3-oxazolidine-2-thiones[4] and 1,3-thiazolidine-2-thiones[5] in aldol reactions have been also evaluated. Recently, Crimmins et al. investigated the diastereoselection in the aldol reaction of *N*-acyl 1,3-oxazolidin-2-ones and thiazolidine-2-thiones in the presence of (−)-sparteine[6] and Evans et al. developed a Ni(II) bis(oxazoline)-catalyzed enantioselective aldol reaction of *N*-propionyl-1,3-thiazolidine-2-thiones in the presence of silyl triflates.[7]

In 1986, Fuentes et al.[8] reported on the addition of boron enolates derived from chiral 1,3-oxazolidin-2-ones to cyclic acylimines. In the same year, Nagao and co-workers described the addition of tin(II) enolates of chiral thiazolidine-2-thiones to *N*-acylimines[9] and *N*-acyliminium ions, which led to the total synthesis of (−)-supinidine,[10] a necine base, which is a constituent of several pyrrolizidine alkaloids.[11] Murahashi and co-workers explored the use of *N*-acyloxy iminium ions prepared from the corresponding nitrones as electrophiles in the addition of boron and titanium(IV) enolates derived from 1,3-oxazolidin-2-ones.[12] Liotta and co-workers investigated the $TiCl_4$ mediated reaction of enolates derived from chiral thiazolidine-2-thiones and non-enolizable imines[13] and *O*-methyl oximes.[14]

We have also reported on the addition of enolates derived from chiral 1,3-oxazolidin-2-ones to 5- and 6-membered *N*-acyliminium ions,[15] a methodology also independently explored by Matsumura et al.[16] In our hands, best diastereoselection was observed when titanium(IV) enolates derived from chiral 1,3-oxazolidin-2-ones reacted with *N*-Boc-2-alkoxypyrrolidines and the preferential *lk* topology was proposed to explain the formation of the major diastereoisomer, a stereochemical outcome analogous to the one described by Nagao and co-workers when tin(II) enolates of chiral *N*-acyl 1,3-thiazolidine-2-one reacted with an endocyclic *N*-acyl iminium ion.[10b]

Our interest on the total synthesis of pyrrolizidine, indolizidine and quinolizidine alkaloids[17] led us to explore the addition of titanium(IV) enolate derived from

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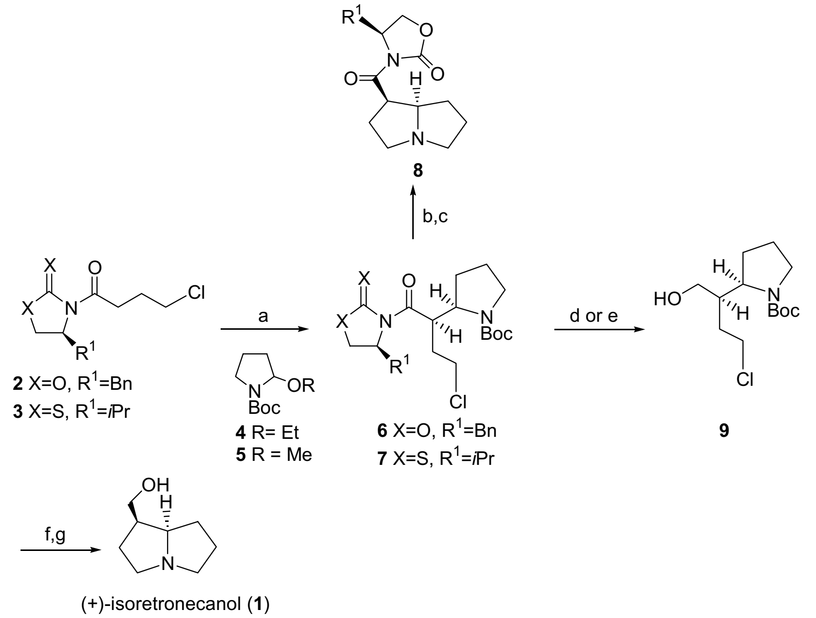
properly *N*-substituted acyl 1,3-oxazolidin-2-one as the precursor for the stereocontrolled construction of the pyrrolizidine motif and (+)-isoretronecanol (**1**), which occurs in Nature in both enantiomeric forms as the corresponding esters and has been isolated from *Planchonella*, *Hammarbya*, *Phalaenopsis* and *Heliotropoium* species[18] was elected as our synthetic target.[19]

Initially, we explored the addition of the titanium(IV) enolate of *N*-4-chlorobutyryl-1,3-oxazolidin-2-one **2** to *N*-Boc-2-ethoxypyrrolidine (**4**) in CH_2Cl_2 at −23 °C. As previously described for analogous transformations,[15] after column chromatography 2-substituted *N*-Boc pyrrolidine **6** was isolated as a single diastereoisomer in 82% yield.[20] With the correct stereochemistry for (+)-isoretronecanol (**1**) secured, we proceeded to construct the pyrrolizidine moiety and recover the chiral auxiliary. Previous removal of the Boc protecting group with TFA in CH_2Cl_2, followed by treatment with satd aq $NaHCO_3$ to liberate the secondary amine for intramolecular nucleophilic substitution provided pyrrolizidine **8** in variable yield (40–70%). Moreover, the hydrolytic (LiOH, H_2O_2, THF, H_2O)[21] or reductive ($NaBH_4$, THF, H_2O) recovery of the chiral auxiliary present in **8** proved to be inefficient due to the competitive nucleophlic attack to the endocyclic carbonyl of 1,3-oxazolidin-2-one **6**. In fact, difficulties associated with the efficient recovery of chiral 1,3-oxazolidin-2-ones from sterically congested substrates have been reported in the literature and we assume that the poor results described here have the same origin (Scheme 1).[22]

In an attempt to circumvent the above problems, we anticipated the removal of the chiral auxiliary, postponing the final ring closure to a later stage. Again, reductive removal of the 1,3-oxazolidin-2-one auxiliary ($NaBH_4$, THF, H_2O) was plagued by low yields and the corresponding alcohol **9** was isolated in 45% yield with by-products resulting from the ring opening of the 1,3-oxazolidin-2-one ring being observed. Additionally, a complex mixture of products was formed when we treated alcohol **9** with TFA in CH_2Cl_2, followed by satd aq $NaHCO_3$ in order to liberate the secondary nitrogen for cyclization.

In order to circumvent the difficulties associated with the removal of the chiral auxiliary, we turned our attention to the use of the titanium (IV) enolate of *N*-4-chlorobutyryl 1,3-thiazolidine-2-thione (**3**) in the coupling step as it is known that these sulfur analogues are more easily cleaved than the corresponding 1,3-oxazolidin-2-ones.[6,23] When **3** was treated with titanium tetrachloride and DIPEA and 2-methoxy-*N*-Boc-pyrrolidine (**5**) was added, 2-substituted pyrrolidine **7** was isolated in 84% yield as a 8:1 mixture with its C-2 epimer (HPLC analysis). The stereochemistry of the major isomer was established after converting the above mixture to the corresponding mixture of alcohols **9** and 2-*epi*-**9** ($LiBH_4$, THF, MeOH) and comparison with an authentic sample of alcohol **9** obtained from **6**. Although an analytical sample of alcohol **9** could be obtained by preparative TLC from **7**, its isolation and recovery of the chiral auxiliary by column chromatography proved to be troublesome due to their coelution in a series of eluting mixture of solvents.

After some experimentation, we found out that (4*S*)-4-isopropyl-1,3-thiazolidine-2-thione could be efficiently recovered after conversion of alcohol **9** to (+)-isoretronecanol (**1**). In the event, **7** was treated with $LiBH_4$ in



Scheme 1. Reagents and conditions: (a) 1. $TiCl_4$, $i Pr_2NEt$, CH_2Cl_2, −23 °C; 2. **4** or **5**, −23 °C (**6**, 82% and **7**, 84%); (b) TFA, CH_2Cl_2; (c) satd aq $NaHCO_3$ (40%, two steps); (d) $NaBH_4$, THF, H_2O (40–50% from **6**); (e) $LiBH_4$, THF, MeOH, 0 °C; (f) TFA, CH_2Cl_2, Et_3SiH; (g) satd aq $NaHCO_3$ (43%, from **7**).

THF/MeOH and the crude product was treated with TFA in CH_2Cl_2 in the presence of Et_3SiH as a *tert*-butyl cation scavenger. After stirring 24 h at rt, the reaction was quenched with $NaHCO_3$ and vigorously stirred with satd aq $NaHCO_3$ for 16 h. After purification of the crude product by column chromatography on neutral alumina, (+)-isoretronecanol (**1**) was isolated in 43% overall yield from **7** and (4*S*)-4-isopropyl-1,3-thiazolidine-2-thione was recovered in 66% yield. The identity of our synthetic sample with (+)-isoretronecanol was established by comparison of its ^1H and ^{13}C NMR spectra and specific optical rotation ($[\alpha]_D^{20} = +71.0$) (c 1.29, EtOH) with those reported in the literature.[19a,g]

In summary, the feasibility of the coupling reaction between the titanium(IV) enolate from of *N*-4-chlorobutyryl 1,3-thiazolidine-2-thiones (**3**) and the exocyclic *N*-acyliminium ion derived from *N*-Boc-2-methoxy pyrrolidine (**4**) has been demonstrated. Despite the lower diastereoselection when compared to the reaction of the titanium(IV) enolate of the corresponding *N*-acyl-1,3-oxazolidin-2-one, the use of 1,3-thiazolidine-2-thiones proved to be beneficial in the recovery of the chiral auxiliary and the total synthesis of (+)-isoretronecanol (**1**) was completed in four steps and 36% overall yield.

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