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Stereoselective formation of optically active 2-oxy-1,3-oxazolidin-4-ones and an efficient synthesis of optically active secondary 2-pyrrolidones

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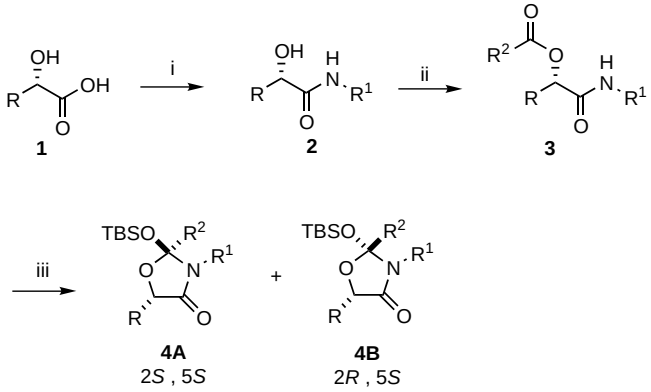
Abstract—Treatment of (–)-*O*-acyllactamides or mandelamides with TBSOTf in the presence of base gives optically active 2-oxy-1,3-oxazolidin-4-ones stereoselectively, which serve as useful precursors for the preparation of optically active secondary 2-pyrrolidones via radical cyclization and subsequent one-step removal of mandelic acid.

Acetals, or their nitrogen analogues, are recognized as a valuable protective group for carbonyl functions[1] and are often used as a powerful device for asymmetric synthesis.[2] Orthoesters and their equivalents,[3] on the other hand, have rarely been used in a similar manner[4] due to their lack of sufficient stability on contact with acidic media, or lack of convenient methods to prepare them in a stereochemically controlled way.[5] Radical cyclization has been recognized as a good tool to construct cyclic compounds.[6] Due to the planar structure of the amide linkage, however, preparation of secondary 2-pyrrolidone with the radical strategy is not usually easy; simple reduction by Bu_3SnH competes.[7] To achieve efficient radical cyclization, introduction of a temporary *N*-substituent or a sterically demanded tether was effective,[8,9] although its removal in the later stage is required.[10] The previously reported asymmetric induction for this cyclization remained at a moderate level.[8] Here we report the first practical and stereoselective synthesis of an optically active nitrogen analogue of cyclic orthoester and their use for a new efficient preparation of optically active secondary 2-pyrrolidones.

Preparation of starting material **3** was achieved by the coupling reactions of lactic or mandelic acid with amines and acids in the presence of EDCI, and desired *O*-acyl-lactamide or -mandelamides were isolated in good yields (Scheme 1). Exposure of **3a** to TBSOTf in the presence of 2,6-lutidine at 0°C, for example, resulted in the rapid disappearance of **3a** and a new compound **4A-a** was formed in a spot-to-spot manner. A 93% yield of compound **4a** was obtained after purification through usual flash chromatography. The results are summarized in Table 1.

To our surprise, **4a** was obtained as an almost single isomer (entry 1). Other mandelic amides **3b–i** also gave



Scheme 1. *Reagents and conditions*: (i) R^1NH_2, EDCI, DMAP; (ii) R_2CO_2H, EDCI, DMAP; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C.

Keywords: chiral auxiliaries; acetals; radical cyclization; heterocycles; ring constructions.

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Table 1. Preparation of optically active 2-oxy-1,3-oxazolidin-4-ones **4**

Entry	R	R^1	R^2	**3** yield (%)[a]	$[\alpha]_D$	**4** yield (%)[a]	**A**/**B**[b]	$[\alpha]_D$[c]
1	Me	1-$C_{10}H_7CH_2$-	Me	**3a**; 91	−81.1	**4a**; 93	99/1	−39.0
2	Ph	Bn	Me	**3b**; 79	+115.4	**4b**; 89	>99/1	+57.2
3	Ph	Bn	Ph	**3c**; 95	+57.8	**4c**; 82	>99/1	−13.5
4	Ph	Bn	*i*-Pr	**3d**; 98	+99.8	**4d**; 97	>99/1	+42.4
5	Ph	CH_2=$CHCH_2$-	Me	**3e**; 67	+57.8	**4e**; 92	96/4	−13.5
6	Ph	CH_2=$CHCH_2$-	$ClCH_2$	**3f**; 51	+93.1	**4f**; 97	69/31	+15.6
7	Ph	CH_2=$CHCH_2$-	$BrCH_2$	**3g**; 90	+78.9	**4g**; 87	63/37	+20.4
8	Ph	CH_2=$CHCH_2$-	$PhSeCH_2$	**3h**; 85	+46.5	**4h**; 88	84/16	+51.1
9	Ph	PhCH=$CHCH_2$-	$PhSeCH_2$	**3i**; 85	+64.8	**4i**; 92	84/16	+35.0

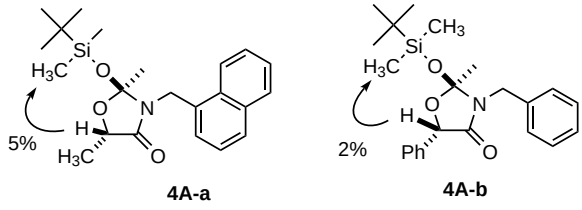
[a] Isolated yield.
[b] Determined by HPLC analyses (Chiral Pak-AD).
[c] Specific rotations for major isomers.

good yields of corresponding **4** (entries 2–9). The stereoselectivity of the reaction depended on the substituent on the *O*-acyl moiety. Acetate derivatives **3b** and **3e**, for example, afforded **4b** and **4e** in a stereoselective manner and diastereomers **4A** were formed as the sole product in each reaction (entries 2 and 5). The present high stereoselectivity was also observed in the conversion of benzoate **3c** and isobutyrate **3d** (entries 3 and 4). Chloroacetate **3f** and bromoacetate **3g**, on the other hand, underwent the formation of a mixture of the two diastereomers in about a 2:1 ratio (entries 6 and 7). Use of phenylselenoacetate **3h** improved the selectivity to 84/16 (entry 8). The two isomers, **4A-h** and **4B-h**, were separated by careful flash chromatographic treatment (silica gel/hexane–ether, 35:1 v/v). The *N*-cinnamyl derivative **4i** was prepared in a similar manner (entry 9).

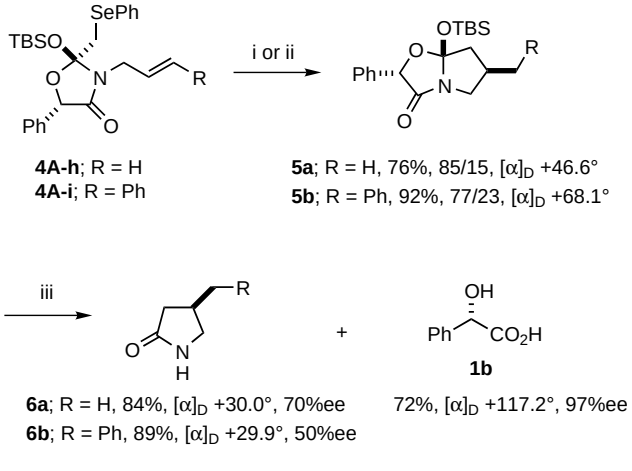
The structure and configuration of **4** were determined in the following way. In a ^{13}C NMR spectrum for **4a**, only one carbonyl peak was observed so that one of the two carbonyl groups in **3a** had been converted to another functional group during the transformation. A new peak that appeared around 110 ppm suggested that **4a** contained an orthoester-type carbon. We assumed **4a** had 2-oxy-1,3-oxazolidin-4-one structure, which was confirmed by X-ray crystallographic analysis.[11] Configuration between C2 and C5 was also determined to be 2*S*,5*S* on the basis of the X-ray analysis. An NOE experiment for **4a** indicated that 5% of the signal enhancement occurred when the H5 was irradiated and a similar enhancement was also observed in other **4** (Scheme 2). In this way, their configuration was determined.

We next examined radical cyclization to convert **4** into bicyclic ring system **5** which will be a precursor of 4-substituted secondary 2-pyrrolidone **6**. Treatment of **4A-h** with Bu_3SnH at 0°C resulted in the smooth formation of bicyclic lactam **5a** in a 76% yield (Scheme 3). No simply reduced product **4e** was observed in the reaction mixture. This was in contrast to the reaction of *N*-allyl-*O*-(phenylseleno)acetylmandelamide **3h** that only gave the deselenated product **3e** quantitatively. The stereoselectivity of the cyclization was 85:15. Cinnamyl amide **4A-i** gave a 92% yield of **5b**.

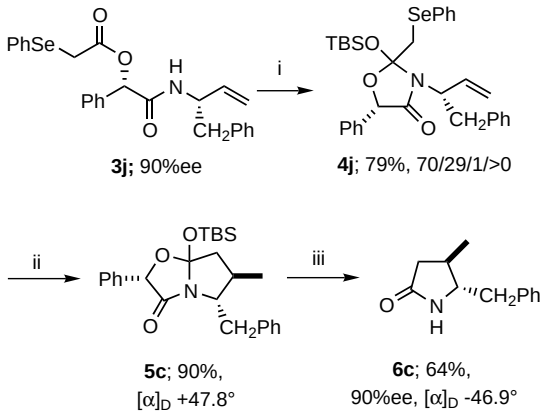
To remove the TBS group, **5a** was treated with TBAF. To our surprise, both of the C–N and C–O bonds in **5a** were simultaneously cleaved and the desired secondary 2-pyrrolidone **6a** was isolated in an 84% yield. The optical purity of **6a** was determined to be 70% ee by a chiral HPLC analysis after the conversion to its *N*-Boc derivative (84%). The positive specific rotation of **6a** clearly indicated that the absolute configuration at C4 was *R*.[12] It should be remarked that mandelic acid was recovered from the reaction mixture with a 72% yield. The recovered mandelic acid showed a positive specific rotation of +117.2°, that indicated no significant loss of optical purity had occurred during the presence of chemical transformation. It should be remarked that this method provides a short preparation of chiral



Scheme 2. NOE experiments for **4A-a** and **4A-b**.



Scheme 3. *Reagents and conditions*: (i) Bu_3SnH, AIBN, toluene, 0°C, hν; (ii) Bu_3SnH, AIBN, toluene, 110°C; (iii) TBAF, THF.



Scheme 4. *Reagents and conditions*: (i) TBSOTf, 2,6-lutidine, 0°C; (ii) Bu_3SnH, AIBN, toluene, 110°C; (iii) TBAF, THF.

monosubstituted secondary 2-pyrrolidones via radical cyclization strategy; neither a temporary *N*-protective group[10] nor an α-substituent that affords chiral induction are required.[8] Optically active 4-benzyl-2-pyrrolidone **6b** was obtained in a similar manner. With this procedure in hand, 4,5-disubstituted-2-pyrrolidone **6c** was examined (Scheme 4). Although a diastereomeric mixture was formed during the conversion to **4** and **5**, desired (4*R*,5*S*)-2-pyrrolidone **6c** was isolated as a single isomer with 90% ee;[13] no separation of diastereomers in **4** and **5** was needed. Thus, the stereoselectivity of the radical cyclization step is quite high.[6c]

In conclusion, we have found a simple and stereoselective method to convert lactic or mandelic amides to 2-oxy-1,3-oxazolidin-4-ones, which serve as a useful precursor to prepare optically active chiral secondary 2-pyrrolidones. This method provides the first use of mandelic acid as a chiral orthester-equivalent auxiliary. Each step of the procedure takes place under mild and neutral conditions, and products are isolated in good yields in a stereoselective manner. Recovered mandelic acid maintained its optical purity so that it opens a way for recycled use. Further investigation and applications are now underway in our laboratory.

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13. Compound **3j** was prepared from (*S*)-L-phenylalanine with 90% ee. *trans*-Configuration in **6c** between C4 and C5 was determined by an NOE experiment. Details will be reported in due course.