Tetrahedron: Asymmetry Vol. 4, No. 8, pp. 1941-1948, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Conjugate Addition of Amines and Thiols to (*R*)-1-Acetyl-5-isopropoxy-3-pyrrolin-2-one; Preparation of Enantiopure *N*-Acyliminium Ion Precursors

Wim-Jan Koot, Henk Hiemstra*, and W. Nico Speckamp*

Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

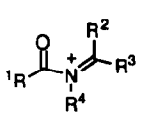
(*Received in UK* 16 *June* 1993)

Abstract: Conjugate addition reactions of amines and thiols to enantiopure (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one are shown to proceed with high stereoselectivity. The benzylamine and the benzyl mercaptan adducts were *N*-deacylated and then treated with Lewis acid to effect *N*-acyliminium cyclization. This cyclization proceeded smoothly with the benzyl mercaptan adduct. The benzylamine adduct only cyclized after amine protection with the Boc group, but then led to an enantiopure oxazolidinone.

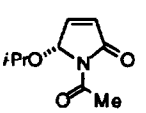
INTRODUCTION

Over the years the *N*-acyliminium ion (**1**) has proven to be a reactive intermediate of great synthetic value, in particular for carbon-carbon bond formation.[1] Because of the growing interest in the synthesis of enantiopure compounds, several publications have appeared about the use of *N*-acyliminium ions for the synthesis of pure enantiomers.[2,3] As the *N*-acyliminium ion (**1**) itself is planar, stereoselectivity has to originate from chirality in the substituents R^1 to R^4. Such a chiral substituent can either be a chiral auxiliary[2] or a non-detachable stereocenter.[3]

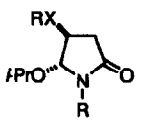
We recently reported the synthesis of the enantiopure building block **2**,[4] which can be converted into a variety of enantiopure cyclic *N*-acyliminium ion precursors. For instance, we demonstrated its applicability in Diels-Alder reactions[4] and conjugate additions of cuprates.[5] Furthermore, the synthesis of the tetracarbonyliron complexes of **2** and the nucleophilic substitution reactions at C5 carried out with these complexes have been described.[6] We wish to report in this paper the addition of amines and thiols to enantiopure **2**. The isopropoxy group was expected to direct the nucleophile to the opposite π-face of the molecule, resulting in selective *trans*-addition. The use of the addition products **3** for *N*-acyliminium ion cyclizations[1] will subsequently be examined, as the *N*-acyliminium ions **5** should be readily accessible from the deacylated products **4**.



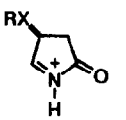
1



2



3 R = Ac
4 R = H



5

Conjugate addition reactions of amines and thiols to enantiopure 5-menthoxy-2[5H]-furanones have recently been published to proceed with high stereoselectivity.[7] For the analogous nitrogen compounds, such addition reactions are only known for racemic 5-methoxy-3-pyrrolin-2-ones, unsubstituted on nitrogen.[8] The reactions of amines with this unsaturated lactam gave a considerable amount of byproducts along with the 1,4-addition products. These byproducts arose from double bond shift to the Δ^4 and Δ^5 position. Based on

literature data and our own experience, these problems were unlikely to occur with **2** due to the electron-withdrawing acetyl substituent on nitrogen.[9] This *N*-acetyl function will also increase the electrophilic character of the double bond so that good reactivity in the 1,4-addition reactions was expected.

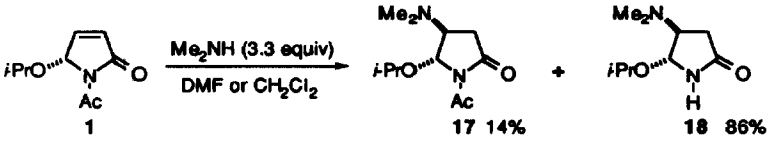
RESULTS AND DISCUSSION

1,4-Addition of amines and thiols

Before investigating the addition reactions of various amines to the enantiopure pyrrolinone **2**, its configurational stability under the basic reaction conditions was checked first. After being stirred in DMF at room temperature in the presence of triethylamine (1.1 equiv) for 72 h, the optical purity of **2** was virtually undiminished (>96% ee).

The additions were carried out with 1.1 equiv of the amine in dichloromethane or DMF as solvent (Table I, entry 1-7). The reactions proceeded with high *trans*-stereoselectivity according to the ^{1}H NMR spectra of the crude products. The addition reactions of piperidine (entry 2), isopropylamine (entry 4) and benzylamine (entry 5 and 6) gave *trans/cis* ratios >12:1, while no *cis*-product could be detected with pyrrolidine (entry 1), diethylamine (entry 3) and neopentylamine (entry 7). The *cis*-products, when formed, could not be obtained pure. In the *trans*-products the vicinal coupling constant of H5 was ca. 0.5 Hz, while the (alleged) *cis*-products showed a coupling constant of ca. 5.5 Hz.[8,10]

The rate of addition reactions were strongly dependent on the structure of the amine. In general, the addition reactions proceeded faster in DMF than in dichloromethane. The reaction mixtures were stirred overnight, although in several cases the reaction was virtually complete after ca. 4 h. The additions involving pyrrolidine and piperidine (entries 1 and 2) proceeded very fast, even in dichloromethane. However, when diethylamine (entry 3) was used, the reaction did not go to completion. This observed decrease in reactivity is probably due to steric interactions, because the reaction of diisopropylamine gave no addition product at all. The 1,4-addition of benzylamine in dichloromethane (entry 5) resulted in the recovery of ca. 50% of starting material. However, the addition reaction proceeded quantitatively in DMF, but also gave 12% of **12** by subsequent deacylation. The reaction with neopentylamine, a primary bulky amine, was carried out in DMF (entry 7), because no reaction was observed in dichloromethane. However, even in DMF this reaction did not go to completion, and the ratio of the compounds **13**:**14**:**2** obtained from this reaction was 73:18:9, respectively.

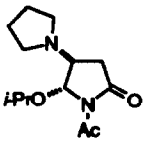
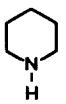
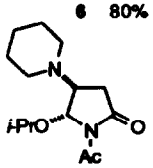
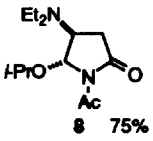
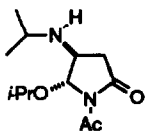
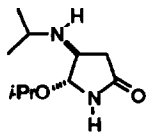
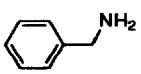
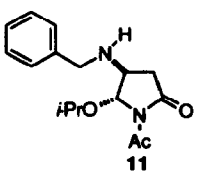
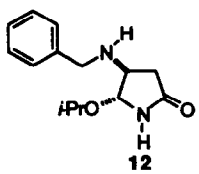
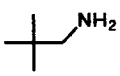
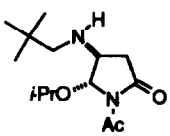
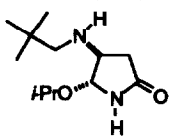
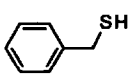
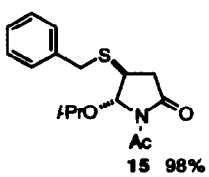
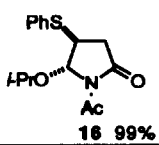


(1)

As can be seen from Table I, an excess of amine can cause deacylation after the addition reaction (entry 4, 6 and 7). It was concluded from the results obtained that conjugate addition occurred prior to deacylation in these reactions, because deacylated **2** could not be detected. When a larger excess of dimethylamine (3.3 equiv) was used (eq 1), the 1,4-addition product **17** was obtained in only 14% after 18 h, whereas the deacylated **18** was formed in 86%. This result shows that dimethylamine is useful for removing the acetyl group from nitrogen.[4-6] In general, it appeared to be very difficult to purify the deacylated products by flash chromatography because of the ease of hydrolysis at C5. However, the deacylated products were obtained almost pure after the deacylation reaction with dimethylamine simply by evaporating the solvent (DMF) in vacuo.

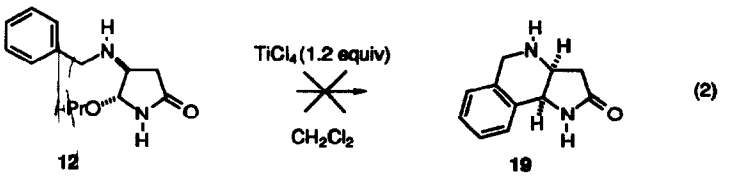
Two different thiols were employed for the 1,4-addition to substrate **2** (entry 8 and 9). No deacylation was observed in both cases. The addition of thiophenol and benzyl mercaptan proceeded quantitatively and with high stereoselectivity, as only a singlet could be found for H5 in the ^{1}H NMR spectra of the crude products.[8,10]

Table I. 1,4 Addition of Amines and Thiols to 2

entry	nucleophile (1.1 equiv)	solvent	product(s) / yield (yield based on ^{1}H NMR)	
1		CH_2Cl_2	 **6** 80% (>95%)	$[\alpha]^{20}_D$ -51 (*c* 0.65, $CHCl_3$) m.p. 47-48 °C
2		CH_2Cl_2	 **7** 91% (>95%)	$[\alpha]^{20}_D$ -19 (*c* 1.31, $CHCl_3$)
3	Et_2NH	CH_2Cl_2	 **8** 75% (75%)	$[\alpha]^{20}_D$ -18 (*c* 0.99, $CHCl_3$)
4		DMF	 **9** 82% (86%)  **10** (14%)	for **9**: $[\alpha]^{20}_D$ -48 (*c* 1.08, $CHCl_3$)
5		CH_2Cl_2	 **11** (50%)  **12**	for **11**: $[\alpha]^{20}_D$ -34 (*c* 0.95, $CHCl_3$)
6		DMF	72% (88%) (12%)	
7		DMF	 **13** 61% (73%)  **14** (18%)	for **13**: $[\alpha]^{20}_D$ -45 (*c* 0.67, $CHCl_3$)
8		CH_2Cl_2	 **15** 98%	$[\alpha]^{20}_D$ -94 (*c* 0.53, $CHCl_3$)
9	PhSH	CH_2Cl_2	 **16** 99%	$[\alpha]^{20}_D$ -65 (*c* 1.08, $CHCl_3$)

N-Acyliminium ion cyclizations

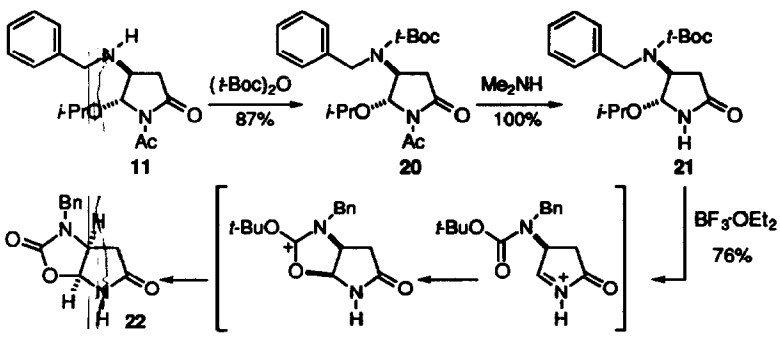
The use of 4-nitrogen-substituted 5-alkoxypyrrolidin-2-ones as precursors in *N*-acyliminium chemistry is unprecedented. Such compounds can be viewed as being derived from 3-nitrogen-substituted succinimides, which in turn are available from aspartic acid.[11] Previous work in our group indicated that hydride reduction methods applied to various 3-nitrogen-substituted succinimides suffered from unsatisfactory regioselectivity.[11] The present methodology provides a useful entry into the aspartic acid derived *N*-acyliminium ion precursors.



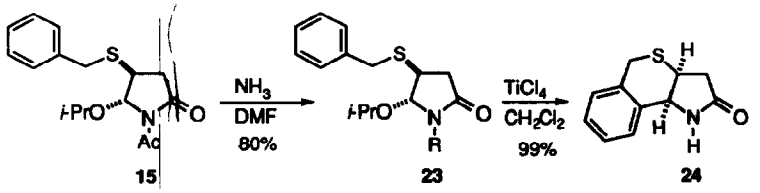
(2)

In order to effect an intramolecular *N*-acyliminium reaction onto the aromatic ring, **12** was treated with 1.2 equiv of $TiCl_4$ in dichloromethane. However, only starting material was recoved, possibly due to complexation of the Lewis acid with the amine thereby deactivating the lactam for cationic chemistry (eq 2). To overcome this problem, the amine function was protected as a carbamate (**20**, Scheme I).

Scheme I



It appeared not possible to prepare **20** through 1,4-addition of *tert*-butyl *N*-benzylcarbamate to **2**. Therefore, lactam **11** was treated with di-*tert*-butyl dicarbonate to give **20** in excellent yield. Lactam **20** was deacylated with dimethylamine (5.5 equiv) to **21**, which subsequently underwent cyclization in the presence of $BF_3{\cdot}OEt_2$. The cyclization product appeared to be **22** {$[\alpha]^{20}_D$ +145 (*c* 0.32, $CHCl_3$), mp 138.5-140 °C} formed through participation of the Boc function. No trace of the desired product **19** was observed. The bicyclic oxazolidinone **22** appeared to be very stable, even towards treatment with $TiCl_4$. Although the desired cyclization product could not be obtained so far, the formation of the oxazolidinone indicates that the desired *N*-acyliminium ion was generated.



(3)

Deacylation of **15** by treatment with ammonia in DMF yielded **23** in 80% after flash chromatograpy (eq 3). This lactam was also used for an *N*-acyliminium cyclization employing $TiCl_4$ (1.5 equiv) as Lewis acid. The tricyclic sulfide **24** {$[\alpha]^{20}_D$ -146 (*c* 0.19, $CHCl_3$), mp 214-214.5 °C} was obtained in virtually quantitative yield.

To summarize, we have shown that (*R*)-**2** is a good substrate for 1,4-addition reactions with amines and thiols, leading to novel enantiopure *N*-acyliminium precursors. Although the *N*-acyliminium ions were formed smoothly with the benzylamine adduct **21** and the benzyl mercaptan adduct **23**, the former led to the formation of the oxazolidinone **22**, whereas the latter afforded the desired tricyclic compound **24**.

ACKNOWLEDGEMENT

This investigation was supported by the Netherlands' Foundation for Chemical Research (SON) with financial aid from the Netherlands' Organization for the Advancement of Pure Research (NWO).

EXPERIMENTAL

General information. Infrared spectra were obtained from $CHCl_3$ solutions using a Perkin-Elmer 298 or Perkin-Elmer 1310 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$ as solvent using a Bruker AC 200 (200 MHz), or a Bruker WM 250 (250 MHz). The Bruker AC 200 and WM 250 instruments were also used for the ^{13}C NMR spectra (50 or 63 MHz) in $CDCl_3$ solution. Chemical shifts are given in ppm downfield from tetramethylsilane. Optical rotations were measured with a Perkin Elmer 241 polarimeter. R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Purification refers to flash chromatography using the same solvent as for TLC and Merck silica gel 60 (230-400 mesh) or Janssen Chimica silica gel (0.030-0.075 mm), unless stated otherwise. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a. d. Ruhr, Germany. Melting points are uncorrected. CH_2Cl_2 was distilled from P_2O_5 and stored over MS 4Å under an atmosphere of dry nitrogen. $TiCl_4$ was distilled and stored under a dry nitrogen atmosphere as a solution in CH_2Cl_2. $BF_3{\cdot}OEt_2$ was distilled and stored under a dry nitrogen atmosphere. Dry DMF was distilled from CaH_2 and stored over MS 4Å under a dry nitrogen atmosphere.

(4*S*,5*R*)-1-Acetyl-5-(1-methylethoxy)-4-(1-pyrrolidinyl)pyrrolidin-2-one (6). A solution of **2** (55 mg, 0.30 mmol) and 2-pyrrolidinone (28 µL, 0.34 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product (72 mg, 95%) was almost pure. Purification (EtOAc/hexanes 1:1.3) yielded **6** in 80% (61 mg, 0.24 mmol) as colorless crystals (m.p. 47-48 °C). R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -51 (*c* 0.65, $CHCl_3$); IR 2970, 2930, 2870, 2800, 1745, 1700, 1370; ^1H NMR (200 MHz): 1.10 & 1.16 (2 × d, 3 H, *J* = 6.1 Hz, CH_3-CH-CH_3), 1.73 (m, 4 H), 2.45 (dd, 1 H, *J* = 1.0, 17.0 Hz, *H*CH-CO), 2.46 (s, 3 H, CH_3-CO), 2.54 (m, 4 H), 2.81 (d, 1 H, *J* = 6.1 Hz, *CH*-CH_2-CO), 2.90 (dd, 1 H, *J* = 6.1, 17.0 Hz, HC*H*-CO), 3.94 (sept, 1 H, *J* = 6.1 Hz, CH_3-*CH*-CH_3), 5.63 (s, 1 H, O-CH-N); ^{13}C NMR (63 MHz): 174.6, 171.3, 86.7, 71.3, 63.6, 51.3 (2 × C), 36.8, 25.2, 23.3 (2 × C), 22.7, 22.6.

(4*S*,5*R*)-1-Acetyl-5-(1-methylethoxy)-4-(1-piperidinyl)pyrrolidin-2-one (7). A solution of **2** (50 mg, 0.27 mmol) and piperidine (30 µL, 0.30 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. Purification (EtOAc/hexanes 1:1.3) yielded **7** in 91% (67 mg, 0.25 mmol) as a colorless oil. R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -19 (*c* 1.31, $CHCl_3$); IR 2970, 2940, 2850, 2800, 1740, 1700, 1370; ^1H NMR (200 MHz): 1.08 & 1.16 (2 × d, 3 H, *J* = 6.1 Hz, CH_3-CH-CH_3), 1.35-1.60 (m, 6 H), 2.24-2.50 (m, 5 H), 2.46 (s, 3 H, CH_3-CO), 2.92 (dd, 1 H, *J* = 8.0, 17.7 Hz, HC*H*-CO), 3.04 (d, 1 H, *J* = 8.0 Hz, *CH*-CH_2-CO), 3.94 (sept, 1 H, *J* = 6.1 Hz, CH_3-*CH*-CH_3), 5.62 (s, 1 H, O-CH-N).

(4*S*,5*R*)-1-Acetyl-4-(*N*,*N*-diethylamino)-5-(1-methylethoxy)pyrrolidin-2-one (8). A solution of **2** (51 mg, 0.28 mmol) and diethylamine (32 µL, 0.31 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product was a mixture of **8** and **2** (75:25). Purification (EtOAc/hexanes 1:1.3) yielded **8** in 75% (53 mg, 0.21 mmol) as a colorless oil. R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -18 (*c* 0.99, $CHCl_3$); IR 2970, 2930, 1740, 1700, 1370; ^1H NMR (200 MHz): 0.96 (t, 6 H, *J* = 7.1 Hz, (CH_3-CH_2)$_2$-N), 1.10 & 1.18 (2 × d, 3 H, *J* = 6.1 Hz, CH_3-CH-CH_3), 2.34-2.48 (m, 5 H, (CH_3-CH_2)$_2$-N & *H*CH-CO), 2.45 (s, 3 H, CH_3-CO), 2.87 (dd, 1 H, *J* = 7.8, 18.2 Hz, HC*H*-CO), 3.23 (dd, 1 H, *J* = 0.6, 7.7 Hz, *CH*-CH_2-CO), 3.93 (sept, 1 H, *J* = 6.1 Hz, CH_3-*CH*-CH_3), 5.50 (s, 1 H, O-CH-N).

(4*S*,5*R*)-1-Acetyl-4-(*N*-isopropylamino)-5-(1-methylethoxy)pyrrolidin-2-one (9). A solution of **2** (50 mg,

0.27 mmol) and isopropylamine (26 μL, 0.30 mmol) in DMF (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product was a mixture of **9** and **10** (86:14). Purification (EtOAc/hexanes 1:1.3) yielded **9** in 82% (54 mg, 0.22 mmol) as a colorless oil. R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -48 (*c* 1.08, $CHCl_3$); IR 2965, 1745, 1695, 1370; ^{1}H NMR (200 MHz): 1.04 (t, 6 H, *J* = 5.8 Hz, C*H*$_3$-CH(N)-C*H*$_3$), 1.11 & 1.18 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH(O)-C*H*$_3$), 2.15 (d, 1 H, *J* = 17.4 Hz, *H*CH-CO), 2.48 (s, 3 H, CH$_3$-CO), 2.87 (sept, 1 H, *J* = 6.3 Hz, CH$_3$-C*H*(N)-CH$_3$), 3.00 (dd, 1 H, *J* = 6.1, 17.5 Hz, HC*H*-CO), 3.25 (d, 1 H, *J* = 6.0 Hz, C*H*-CH$_2$-CO), 3.95 (sept, 1 H, *J* = 6.1 Hz, CH$_3$-C*H*-CH$_3$), 5.42 (s, 1 H, O-CH-N).

(4*S*,5*R*)-1-Acetyl-4-(*N*-benzylamino)-5-(1-methylethoxy)pyrrolidin-2-one (11). A solution of **2** (55 mg, 0.30 mmol) and benzylamine (36 μL, 0.33 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product was a mixture of **2** and **11** (~1:1) and was not purified further.

A solution of **2** (50 mg, 0.27 mmol) and benzylamine (33 μL, 0.30 mmol) in DMF (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product (78 mg, 98%) was a mixture of **11** and **12** (88:12). Purification (EtOAc/hexanes 1:1.3) yielded **11** in 72% (57 mg, 0.20 mmol) as a colorless oil. R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -34 (*c* 0.95, $CHCl_3$); IR 2970, 2930, 1745, 1695, 1368; ^{1}H NMR (200 MHz): 1.13 & 1.17 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.24 (d, 1 H, *J* = 17.5 Hz, *H*CH-CO), 2.51 (s, 3 H, CH$_3$-CO), 3.02 (dd, 1 H, *J* = 6.0, 17.4 Hz, HC*H*-CO), 3.23 (d, 1 H, *J* = 5.9 Hz, C*H*-CH$_2$-CO), 3.83 (s, 2 H, CH$_2$-N), 3.95 (sept, 1 H, *J* = 6.1 Hz, CH$_3$-C*H*-CH$_3$), 5.51 (s, 1 H, O-CH-N), 7.29 (m, 5 H, Ph); ^{13}C NMR (50 MHz): 174.6, 171.6, 139.1, 128.6 (2 × C), 128.0 (2 × C), 127.4, 88.0, 71.5, 56.8, 51.4, 39.0, 25.2, 22.7, 22.5.

(4*S*,5*R*)-1-Acetyl-4-(*N*-(2,2-dimethylpropyl)amino)-5-(1-methylethoxy)pyrrolidin-2-one (13). A solution of **2** (52 mg, 0.28 mmol) and 2,2-dimethylpropylamine (35 μL, 0.30 mmol) in DMF (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product was a mixture of **13**, **14** and **2** (73:18:9). Purification (EtOAc/hexanes 1:1.3) yielded **13** in 61% (47 mg, 0.17 mmol) as a colorless oil. R_f 0.35 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -45 (*c* 0.67, $CHCl_3$); IR 2965, 1745, 1695, 1370; ^{1}H NMR (200 MHz): 0.85 (s, 9 H, (CH$_3$)$_3$-C), 1.13 & 1.20 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.17 (dd, 1 H, *J* = 0.6, 17.4 Hz, *H*CH-CO), 2.36 (s, 2 H, CH$_2$-N), 2.50 (s, 3 H, CH$_3$-CO), 3.00 (dd, 1 H, *J* = 5.8, 17.0 Hz, HC*H*-CO), 3.12 (d, 1 H, *J* = 5.8 Hz, C*H*-CH$_2$-CO), 3.97 (sept, 1 H, *J* = 6.1 Hz, CH$_3$-C*H*-CH$_3$), 5.42 (s, 1 H, O-CH-N).

(4*S*,5*R*)-1-Acetyl-4-(benzylthio)-5-(1-methylethoxy)pyrrolidin-2-one (15). A solution of **2** (102 mg, 0.56 mmol), benzylmercaptan (68 μL, 0.58 mmol) and Et$_3$N (84 μL, 0.60 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 5 h and the reaction mixture was concentrated *in vacuo*. The crude product (177 mg) was almost pure. Purification (EtOAc/hexanes 1:1.3) yielded **15** in 98% (168 mg, 0.55 mmol) as a colorless oil. R_f 0.40 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -94 (*c* 0.53, $CHCl_3$); IR 2970, 1745, 1700, 1370; ^{1}H NMR (200 MHz): 1.07 & 1.08 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.33 (d, 1 H, *J* = 17.1 Hz, *H*CH-CO), 2.48 (s, 3 H, CH$_3$-CO), 3.07 (d, 1 H, *J* = 7.4 Hz, *H*C-CH$_2$-CO), 3.17 (dd, 1 H, *J* = 7.4, 17.3 Hz, HC*H*-CO), 3.78 (m, 3 H, CH$_3$-C*H*-CH$_3$ & C*H*$_2$-S), 5.51 (s, 1 H, O-CH-N), 7.29 (m, 5 H, Ph).

(4*S*,5*R*)-1-Acetyl-5-(1-methylethoxy)-4-(phenylthio)pyrrolidin-2-one (16). A solution of **2** (997 mg, 5.44 mmol), Et$_3$N (0.80 mL, 5.76 mmol) and thiophenol (0.60 mL, 5.88 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 2 h and the reaction mixture was concentrated *in vacuo*. The crude product (1.60 g, 100%) was almost pure. Purification (EtOAc/hexanes 1:1.3) yielded **16** in 99% (1.59 g, 5.43 mmol) as a colorless oil. R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -65 (*c* 1.08, $CHCl_3$); IR 2970, 1750, 1700, 1370; ^{1}H NMR (200 MHz): 0.96 & 1.03 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.42 (s, 3 H, CH$_3$-CO), 2.42 (d, 1 H, *J* = 18.2 Hz, *H*CH-CO), 3.24 (dd, 1 H, *J* = 7.4, 18.2 Hz, HC*H*-CO), 3.55 (d, 1 H, *J* = 7.4 Hz, C*H*-CH$_2$-CO), 3.78 (sept, 1 H, *J* = 6.1 Hz, CH$_3$-C*H*-CH$_3$), 5.50 (s, 1 H, O-CH-N), 7.29 (m, 3 H, Ph), 7.40 (m, 2 H, Ph); ^{13}C NMR (50 MHz): 173.3, 171.2, 133.3 (2 × C), 131.8, 129.3 (2 × C), 128.5, 88.6, 71.8, 45.0, 37.6, 25.0, 22.5, 22.2.

(4*S*,5*R*)-1-Acetyl-4-(*N*,*N*-dimethylamino)-5-(1-methylethoxy)pyrrolidin-2-one (17) and (4*S*,5*R*)-4-(*N*,*N*-dimethylamino)-5-(1-methylethoxy)pyrrolidin-2-one (18). A solution of **2** (50 mg, 0.27 mmol) and dimethylamine (60 μL, 0.90 mmol) in DMF (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product was a 1:6 mixture of **17** and **18**, respectively (52 mg, 100%).

A solution of **2** (50 mg, 0.27 mmol) and dimethylamine (60 μL, 0.90 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 18 h and the reaction mixture was concentrated *in vacuo*. The crude product was a 1:6 mixture of **17** and **18**. Purification (EtOAc/hexanes 1:1.3) yielded **17** in 14% (9 mg, 0.04 mmol) as a colorless oil. For **17**: R_f 0.30 (EtOAc/hexanes 1:1.3); $[\alpha]^{20}_D$ -36 (*c* 0.40, $CHCl_3$); IR 2970, 2930, 2870, 2830, 2780, 1740, 1700, 1370; ^{1}H NMR (200 MHz): 1.13 & 1.19 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.24 (s, 6 H, (CH$_3$)$_2$-N) 2.48 (m, 1 H, *H*CH-CO), 2.49 (s, 3 H, CH$_3$-CO), 2.89 (dd, 1 H, *J* = 7.2, 9.7 Hz, HC*H*-CO), 2.94 (d, 1 H, *J* = 7.4 Hz, C*H*-CH$_2$-CO), 3.97 (sept, 1 H, *J* = 6.1 Hz, CH$_3$-C*H*-CH$_3$), 5.66 (s, 1 H, O-CH-N). For **18** (from crude product): ^{1}H NMR (200 MHz): 1.13 (d, 6 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.20 (dd, 1 H, *J* = 4.6, 17.5 Hz, *H*CH-CO), 2.20 (s, 6 H, (CH$_3$)$_2$-N), 2.51 (dd, 1 H, *J* = 8.5, 17.5 Hz, HC*H*-CO), 3.00 (m, 1 H, C*H*-CH$_2$-CO), 3.72 (sept, 1 H, *J* = 6.1 Hz, CH$_3$-C*H*-CH$_3$), 4.91 (d, 1 H, *J* = 1 Hz, O-CH-N), 8.14 (s(br), 1 H, N-H).

(4*S*,5*R*)-1-Acetyl-4-(*N*-benzyl-*N*-(1,1-dimethylethoxycarbonyl)amino)-5-(1-methylethoxy)pyrrolidin-2-one (20). A solution of **11** (213 mg, 0.54 mmol), di-*tert*-butyl dicarbonate (142 mg, 0.65 mmol) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 3 h. The solution was poured onto saturated aqueous NH_4Cl (10 mL), and the water layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*. Purification (EtOAc) yielded **20** in 87% (183 mg, 0.47 mmol) as colorless crystals. Recrystallization (hexanes) gave 147 mg of **20** (70%) as colorless crystals: m.p. 71.5-72.5 °C. R_f 0.40 (EtOAc); $[\alpha]^{20}_D$ +14 (*c* 1.21, $CHCl_3$); IR 2970, 1740, 1690 (vs), 1365; ^{1}H NMR (200 MHz): 1.07 & 1.08 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 1.43 (s, 9 H, $(CH_3)_3$-C), 2.37 (s, 3 H, CH_3-CO), 2.43 (d(br), 1 H, *H*CH-CO), 2.85 (dd, 1 H, *J* = 9.3, 18.3 Hz, HC*H*-CO), 3.90 (m, 2 H, CH_3-C*H*-CH_3 & C*H*-CH_2-CO), 4.22 (d, 1 H, *J* = 15.9 Hz, *H*CH-N), 4.62 (d(br), 1 H, HC*H*-N), 5.43 (s, 1 H, O-CH-N), 7.24 (m, 5 H, Ph); ^{13}C NMR (50 MHz): 173.7, 170.9, 155.0, 138.0, 128.8 (2 × C), 127.7 (2 × C), 127.1, 90.4, 72.1, 57.3, 51.2, 28.3, 25.5, 23.0, 22.3; Anal. Calcd. for $C_{21}H_{30}N_2O_5$: C, 64.60; H,7.74; N, 7.17. Found: C, 64.73; H,7.81; N, 7.20.

Oxazolidinone 22 via 21. A solution of **20** (121 mg, 0.31 mmol) and dimethylamine (110 µL, 1.66 mmol) in DMF (2 mL) was stirred at rt for 18 h and the solvent was removed *in vacuo*. {spectral data for **21**: IR 3430, 3300, 2970, 1700 (shoulder), 1685; ^{1}H NMR (200 MHz): 1.02 & 1.08 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 1.46 (s, 9 H, $(CH_3)_3$-C), 2.46 (s(br), 1 H, *H*CH-CO), 2.53 (dd, 1 H, *J* = 9.4, 17.3 Hz, HC*H*-CO), 3.57 (t(br), 1 H, CH_3-C*H*-CH_3), 3.87 (s(br), 1 H, C*H*-CH_2-CO), 4.38 & 4.52 (2 × d, 1 H, *J* = 15.6 Hz, CH_2-N), 5.02 (s(br), 1 H, O-CH-N), 7.26 (m, 5 H, Ph), 7.90 (s(br), 1 H, OC-N-H)}. The crude product was dissolved in CH_2Cl_2 (5 mL) and BF_3·OEt_2 (80 µL, 0.66 mmol) was added at rt. This solution was stirred for 18 h and quenched with saturated aqueous $NaHCO_3$ (5 mL). The water layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and purification (EtOAc) yielded **22** in 76% (55 mg, 0.24 mmol) as a white solid. Recrystallization (EtOAc/hexanes 10:1) gave 36 mg of white crystals (50%): m.p. 138.5-140 °C. R_f 0.15 (EtOAc); $[\alpha]^{20}_D$ +145 (*c* 0.32, $CHCl_3$); IR 3430, 1755, 1720; ^{1}H NMR (250 MHz): 2.42 (d, 2 H, *J* = 4.9 Hz, CH_2-CO), 4.10 (d, 1 H, *J* = 15.1 Hz, *H*CH-N), 4.22 (m, 1 H, C*H*-CH_2-CO), 4.78 (d, 1 H, *J* = 15.1 Hz, HC*H*-N), 5.82 (d, 1 H, *J* = 7.1 Hz, O-CH-N), 7.31 (m, 6 H, Ph & N-H); ^{13}C NMR (50 MHz): 174.3, 155.8, 134.6, 129.1 (2 × C), 128.4, 128.3 (2 × C), 82.6, 53.6, 46.8, 33.9; Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.02; H, 5.17; N, 12.03.

(4*S*,5*R*)-4-(Benzylthio)-5-(1-methylethoxy)pyrrolidin-2-one (23). A stream of ammonia was bubbled through a solution of **15** (166 mg, 0.54 mmol) in DMF (2 mL) for 18 h. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (EtOAc/hexanes 1.3:1) yielding **23** in 80% (115 mg, 0.43 mmol). R_f 0.20 (EtOAc/hexanes 1.3:1); IR 3440, 2970, 1705; ^{1}H NMR (200 MHz): 1.11 & 1.12 (2 × d, 3 H, *J* = 6.1 Hz, C*H*$_3$-CH-C*H*$_3$), 2.12 (dd, 1 H, *J* = 3.4, 17.7 Hz, *H*CH-CO), 2.82 (dd, 1 H, *J* = 8.5, 17.7 Hz, HC*H*-CO), 3.15 (m, 1 H, *H*C-CH_2-CO), 3.64 (sept, 1 H, *J* = 6.1 Hz, CH_3-C*H*-CH_3), 3.73 & 3.81 (2 × d, 1 H, *J* = 13.5 Hz, CH_2-S), 4.86 (s, 1 H, O-CH-N), 7.28 (m, 5 H, Ph), 8.19 (s(br), 1 H, N-H).

[3a*S*-(3aβ,9bβ)]-1,3,3a,4,5,9b-Hexahydro-4-thia-2*H*-benz(g)indol-2-one (24). A 1.1 M solution of $TiCl_4$ in CH_2Cl_2 (0.60 mL, 0.66 mmol) was added to a solution of **23** (115 mg, 0.43 mmol) in CH_2Cl_2 at -78 °C. After 5 min the solution was allowed to come to rt and stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the water layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*, yielding 88 mg of **24** as white crystals (99%). The crude product was almost pure. Recrystallization (EtOAc) gave 70 mg of white crystals (80%): m.p. 214-214.5 °C. $[\alpha]^{20}_D$ -146 (*c* 0.19, $CHCl_3$); IR 3440, 2990, 1695; ^{1}H NMR (200 MHz): 2.48 (dd, 1 H, *J* = 3.9, 17.3 Hz, *H*CH-CO), 2.94 (dd, 1 H, *J* = 8.0, 17.3 Hz, HC*H*-CO), 3.63 (d, 1 H, *J* = 15.3, *H*CH-S), 3.77 (d, 1 H, *J* = 15.3, HC*H*-S), 3.95 (m, 1 H, C*H*-CH_2-CO), 4.92 (d, 1 H, *J* = 6.5 Hz, HC-N), 6.80 (d(br), 1 H, *J* = 8.6 Hz, N-H), 7.22 (m, 4 H, Ar); Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40. Found: C, 64.59; H, 5.51.

REFERENCES AND NOTES

1. For reviews, see: (a) De Koning, H.: Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed; Bioactive Natural Products (Part A), Elsevier, Amsterdam, 1993, Vol. 13, pp 473-518. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.5. (c) Zaugg, H. E. *Synthesis* **1984**, pp 85-110, pp 181-212.
2. (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989; Vol. 7, Chapter 1 and references cited herein. (b) Ermert, P.; Meyer, I.; Stucki, C.; Schneebeli, J.; Obrecht, J.-P. *Tetrahedron Lett.* **1988**, *29*, 1265. (c) Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891. (d) Wanner, K. Th.; Kärtner, A.; Wadenstorfer, E. *Heterocycles* **1988**, *27*, 2549. (e) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525. (f) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215. (g) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (h) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858. (i) Fray, A. H.; Meyers, A. I. *Tetrahedron Lett.* **1992**, *33*, 3575. (j) Arai, Y.; Kontani, T.; Koizumi, T. *Tetrahedron: Asymm.* **1992**, *3*, 535.
3. (a) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Org.*

Chem. **1983**, *105*, 3653. (c) Wijnberg, B. P. *Model Studies on Chiral N-Acyliminium Ions and ω-Carbinollactams*, Thesis, University of Amsterdam, **1985**. (d) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. (e) Thaning, M.; Wistrand, L.-G. *Helv. Chim. Acta* **1986**, *69*, 1711. (f) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590. (g) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. (h) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290. (i) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588. (j) Heitz, M. P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591. (k) Thaning, M.; Wistrand, L.-G. *J. Org. Chem.* **1990**, *55*, 1406. (l) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C, Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949. (m) Koot, W.-J.; Van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401. (n) Skrinjar, M.; Nilsson, C.; Wistrand, L.-G. *Tetrahedron: Asymm.* **1992**, *3*, 1263.

4. Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 1059.
5. Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1992**, *33*, 7969.
6. Koot, W.-J.; Hiemstra, H; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1993**, 156.
7. De Lange, B.; Feringa, B. L. *Tetrahedron* **1988**, *44*, 7213.
8. Jiménez, M. D.; Ortega, R.; Tito, A.; Fariña, F. *Heterocycles* **1988**, *27*, 173.
9. Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1978**, *43*, 376.
10. (a) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177. (b) ref 3h, 3k, 3l, 3m.
11. Wildschut, S.; Mooleaar, M.J.; Hiemstra, H.; Speckamp, W.N. Unpublished results.