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[11] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-151679 (**3a**) and -151680 (**3d**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Enantioselective Hydrogen Atom Transfer Reactions: Synthesis of *N*-Acyl-α-Amino Acid Esters**

Mukund P. Sibi,* Yasutomi Asano, and Justin B. Sausker

Enantioselective proton-transfer reactions (enolate protonations) have been investigated in detail for over a decade and even catalytic variants have been demonstrated.[1] In contrast, enantioselective hydrogen atom transfer reactions have begun to emerge only recently.[2] In principle, these reactions can be carried out in two distinct ways: 1) by H-atom transfer from a chiral reagent to a radical, or alternatively 2) by H-atom transfer from an achiral reagent to a radical complexed to a chiral source. Nanni and Curran,[3a] Metzger and co-workers,[3b,c] Roberts and co-workers,[3d] and Schiesser and co-workers[3e] have reported examples of reactions using chiral H-atom transfer reagents. On the other hand, only a few examples of H-atom transfer to radicals complexed to chiral Lewis acids have been noted in the literature.[4] We have shown that enantioselective conjugate additions proceed with high chemical efficiency and selectivity using a chiral Lewis acid derived from M^{2+} metal salts in conjunction with a bisoxazoline prepared from aminoindanol.[5] Herein we show that conjugate radical addition to *N*-acylamido acrylates **1** mediated by a chiral Lewis acid followed by an enantioselective H-atom transfer furnishes a variety of α-amino acid derivatives (**2** or **3**) with good to excellent efficiency [Eq. (1)].

Diastereoselective H-atom transfer reactions to captodative radicals derived from *N*-acylamido acrylates in both acyclic[6] and cyclic[7] systems proceed with moderate to good selectivity.[8] In contrast, enantioselective variants of these reactions have not been reported and this work constitutes the first example of such a process. We began our experiments

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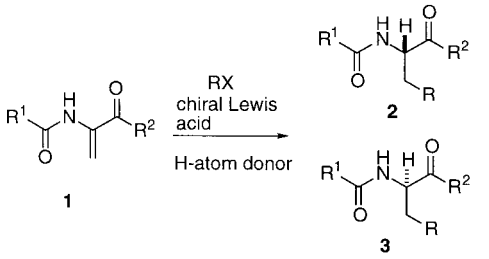


(1)

with the addition of an ethyl radical to differentially substituted α-amino acrylates. Preliminary experiments were designed to arrive at the optimal substitution at the nitrogen and the ester oxygen atoms for chemical efficiency as well as selectivity. The following reaction conditions were used as standard conditions: five equivalents of ethyl iodide/two equivalents of tributyltin hydride, triethylborane/O_2 as an initiator, and with CH_2Cl_2 as the solvent at $-78\,^{\circ}C$. A preliminary non-Lewis acid mediated reaction indicated that conjugate addition was not facile at low temperature ($<5\,\%$ yield of the product after 3 h). The addition of a Lewis acid facilitated the addition. A chiral Lewis acid (1.3 equiv) derived from magnesium perchlorate and bisoxazoline (**4**) was employed in the initial screening experiments [Eq. 2, Table 1].[9] *N*-Benzoyl and benzyloxycarbonyl (CBZ) substituents were not effective (entries 1 and 2). Of the four different *N*-acyl groups investigated the 2-naphthoyl substituent gave the highest *ee* value of 85 % (entry 4). It is interesting to note that the corresponding 1-naphthoyl substituent gave much lower selectivity (entry 3). The next series of experiments examined the effect of the ester substituent. Of the three variations the smaller methyl group in conjunction with the *N*-2-naphthoyl group furnished the highest *ee* values (entries 4–6). Having settled on the *N*-acyl and ester substituents, a brief study of the Lewis acid was undertaken. Of the different Lewis acids investigated $Mg(ClO_4)_2$ gave the highest selectivity as well as chemical yield (compare entry 4 with entries 7–10). Variations in the stoichiometry and/or the nature of the tin H-atom transfer reagent did not show any improvements in the selectivity (entries 10–13). Tris(trimethylsilyl)silane was ineffective as a H-atom transfer reagent (entry 14).

The addition of a variety of nucleophilic radicals of various size and functionality to **1d** under the optimal conditions was undertaken [Eq. (3); Table 2]. Examination of the data in

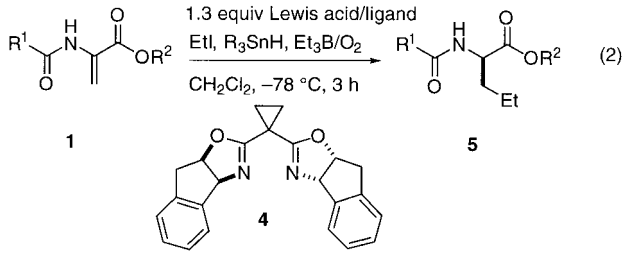
Table 2. Conjugate radical addition to dehydroalanines followed by enantioselective H-atom transfer.[a]

(3)

Entry	RX	Prod.	Yield [%][b]	*ee* [%] (config.)[c]
1	AcBr	**6**	76	80
2	$MeOCH_2Br$	**7**	71	65
3	EtI	**8**	72	85 (*R*)
4	*i*BuI	**9**	76	79
5	*i*PrI	**10**	62	83 (*R*)
6	*c*HexI	**11**	62	55 (*R*)
7	*t*BuI	**12**	54	27 (*R*)

[a] For the general reaction conditions see the Supporting Information. *c*Hex = cyclohexyl. [b] Yields are for isolated products and materials purified by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. For the establishment of the configuration see the Supporting Information.

Table 1. Enantioselective H-atom transfer to glycine radicals: Effect of the *N*-acyl and ester substituents on the selectivity.[a]



(2)

Entry	Compd	R^1	R^2	Lewis acid	H-Atom donor (equiv)	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	Me	$Mg(ClO_4)_2$	Bu_3SnH (2)	62	17
2	**1b**	OBn	Me	$Mg(ClO_4)_2$	Bu_3SnH (2)	61	22
3	**1c**	1-naph	Me	$Mg(ClO_4)_2$	Bu_3SnH (2)	55	47
4	**1d**	2-naph	Me	$Mg(ClO_4)_2$	Bu_3SnH (2)	72	85
5	**1e**	2-naph	Bn	$Mg(ClO_4)_2$	Bu_3SnH (2)	57	68
6	**1f**	2-naph	*t*Bu	$Mg(ClO_4)_2$	Bu_3SnH (2)	56	71
7	**1d**	2-naph	Me	$MgBr_2$	Bu_3SnH (2)	57	27
8	**1d**	2-naph	Me	MgI_2	Bu_3SnH (2)	36	16
9	**1d**	2-naph	Me	$Mg(OTf)_2$	Bu_3SnH (2)	33	3
10	**1d**	2-naph	Me	$Zn(OTf)_2$	Bu_3SnH (2)	42	0
11	**1d**	2-naph	Me	$Mg(ClO_4)_2$	Bu_3SnH (10)	79	84
12	**1d**	2-naph	Me	$Mg(ClO_4)_2$	Ph_3SnH (2)	50	85
13	**1d**	2-naph	Me	$Mg(ClO_4)_2$	Ph_3SnH (5)	77	83
14	**1d**	2-naph	Me	$Mg(ClO_4)_2$	$(TMS)_3SiH$ (2)	6	14

[a] For general reaction conditions see the Supporting Information. Naph = naphthyl. [b] Yields are determined on isolated products and materials purified by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

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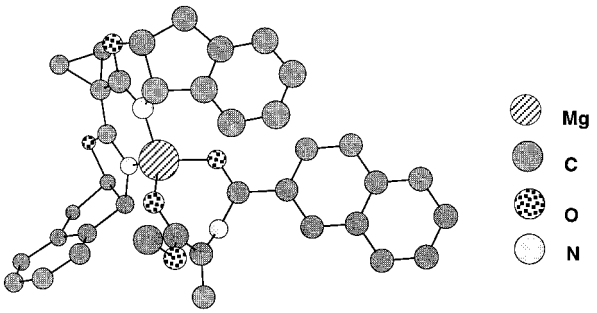
Table 2 indicate that acetyl (entry 1), α-alkoxyalkyl (entry 2), primary alkyl (entries 3 and 4), secondary alkyl (entry 5), and cycloalkyl (entry 6) all show good selectivity in H-atom transfer. However, the bulky *tert*-butyl radical provided low selectivity (entry 7). The low selectivity for **12** may suggest that the bulky *tert*-butyl group and chiral Lewis acid shield opposite faces and reactions may occur from a monocoordinated or noncomplexed substrate.[10]

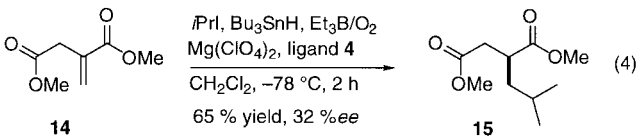
The coordination of the Lewis acid is essential for activating the substrate for conjugate addition (see above). However, the enantioselective H-atom transfer step is subsequent to the radical addition. It is assumed that the structure of the intermediate radical resembles that of the starting complex. The absolute stereochemistry of several products were determined in order to arrive at a working model for the sense of the stereoinduction in the H-atom transfer reactions.[11] On the basis of these results, a conjugate addition to a seven-membered chelate ternary complex (**13**, starting material+ligand+Lewis acid; Figure 1)[12][13] followed by a H-atom transfer is consistent with the observed stereochemistry.[14] H-atom transfer to a monodentate complex and/or the flexibility of the seven-membered chelate could lead to the erosion of selectivity. The variation in *ee* values with changes in the *N*-acyl substituent however cannot be readily understood from the proposed model.[15]



13

Figure 1. 7-Membered chelate. Shielding of the *Re*-face is observed.

To further corroborate the possibility of a seven-membered chelate, the addition of an isopropyl radical to itaconate **14** under the optimal conditions was investigated [Eq. (4)]. The



14 **15** (4)

product from this experiment shows a moderate *ee* value (32%) with an *S* configuration.[16] The absolute stereochemistry of **15** is consistent with a model in which H-atom transfer occurs through a seven-membered chelate similar to **13**.

In conclusion, we have shown that chiral Lewis acid mediated conjugate radical addition to dehydroalanines followed by enantioselective H-atom transfer proceeds with moderate to excellent selectivity to provide α-amino acids. Extension of the methodology to the preparation of C-glycosides and radical addition to β-substituted substrates is underway. The examination of complexes such as **13** as dienophiles in enantioselective Diels–Alder reactions is also underway.

Received: November 16, 2000 [Z16119]

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[11] See Supporting Information.

[12] In this model a tetrahedral arrangement around the magnesium ion is assumed. Alternative five- and six-coordinate complexes are also possible. A definitive statement regarding the structure of the reactive complex is not possible from the data available at present.

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J. O. Metzger, *Angew. Chem.* **2000**, *112*, 2898; *Angew. Chem. Int. Ed.* **2000**, *39*, 2758.

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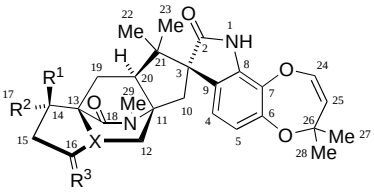

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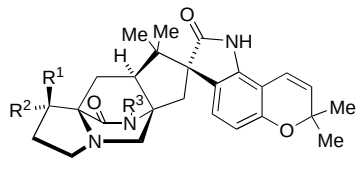

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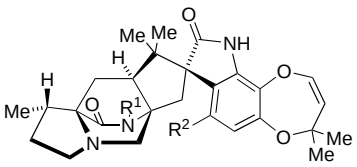

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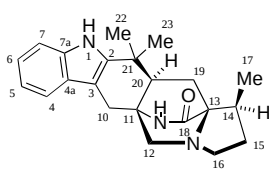

13, VM55599

Figure 1. **1**, paraherquamide A: $R^1 = OH$, $R^2 = Me$, $R^3 = H_2$, $X = N$; **2**, paraherquamide B: $R^1 = H$, $R^2 = H$, $R^3 = H_2$, $X = N$; **3**, paraherquamide C: $R^1 = R^2 = CH_2$, $R^3 = H_2$, $X = N$; **4**, paraherquamide D: $R^1 = O$, $R^2 = CH_2$, $R^3 = H_2$, $X = N$; **5**, VM55596: $R^1 = OH$, $R^2 = Me$, $R^3 = H_2$, $X = N^+\text{-}O^-$; **6**, VM55597: $R^1 = OH$, $R^2 = Me$, $R^3 = O$, $X = N$; **7**, paraherquamide E (VM54159): $R^1 = Me$, $R^2 = H$; **8**, SB203105: $R^1 = Me$, $R^2 = OH$; **9**, SB200437: $R^1 = H$, $R^2 = H$; **10**, paraherquamide F (VM55594): $R^1 = H$, $R^2 = Me$, $R^3 = Me$; **11**, paraherquamide G (VM54158): $R^1 = OH$, $R^2 = Me$, $R^3 = Me$; **12**, VM55595: $R^1 = H$, $R^2 = Me$, $R^3 = H$.

Studies on the Biosynthesis of Paraherquamide: Synthesis and Incorporation of a Hexacyclic Indole Derivative as an Advanced Metabolite**

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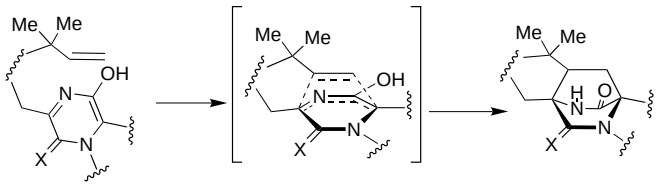
The paraherquamides (Figure 1),[1] along with the brevianamides,[2] marcfortines,[3] and sclerotamides[4] are indolic fungal metabolites that share the common structural feature of an unusual bicyclo[2.2.2]diazaoctane core. It has been postulated that the bicyclo[2.2.2]diazaoctane ring system arises through an intramolecular hetero Diels–Alder cycloaddition of the isoprene moiety across the α-carbons of the amino acid subunits, as shown in Scheme 1.[5]

In 1993, Everett and co-workers isolated a very minor metabolite that also possesses the bicyclo[2.2.2]diazaoctane core, VM55599 (**13**, Figure 1), from *Penicillium* sp. (IMI 332995) which produces paraherquamide A.[6] Based on



Scheme 1. Proposed formation of the bicyclo[2.2.2]diazaoctane ring system in the paraherquamides.

the structural similarities of these co-metabolites, Everett et al. speculated that VM55599 might be a biosynthetic precursor to paraherquamide A.[6] The relative stereochemistry of VM55599 as shown in Figure 1 was assigned by ^{1}H NMR spectroscopy with nuclear Ovenhauser enhancements but the absolute configuration of this substance remains unknown. The stereochemistry of the methyl group in the β-methylproline ring was assigned as being *syn* to the bridging isoprene moiety. In all other known members of the paraherquamide family, the methyl group in the β-methylproline ring is disposed *anti* to the bridging isoprene moiety. If VM55599 was indeed a precursor to paraherquamide A, then oxidation of the β-methylproline ring would have to occur with inversion of stereochemistry at the C-14 center that bears the methyl group.

Previous studies from this laboratory on the biosynthesis of paraherquamide A demonstrated that L-isoleucine is the precursor to the β-methyl-β-hydroxy proline ring of paraherquamide A.[7] The relative disposition of the methyl group in the prolyl ring is retained in the biosynthetic conversion of L-isoleucine into paraherquamide A and, thus, the hydroxylation at C-14 occurs with net retention. These findings bring into question the potential intermediacy of VM55599 in the biosynthesis of the paraherquamides. Furthermore, if L-isoleucine is also the precursor to VM55599, then the absolute stereochemistry of this metabolite must be that depicted in

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