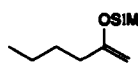
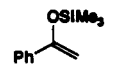
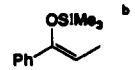
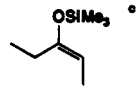
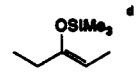
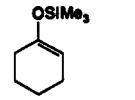
Table I. CAB-Catalyzed Asymmetric Aldol Reactions of Ketone Silyl Ethers with Aldehydes[a]

entry	silyl ethers	RCHO[e]	yield (%)	erythro /threo	ee(%)[j,k] (config)
1		A	81	-	85(I)
2		B	70	-	80(I)
3		A	98	-	85(R)
4		C	88	-	83(I)
5	 [b]	A	86	95/ 5	95(I)
6		D	62	88/12[l]	80(I)
7	 [c]	A	96	94/ 6	96(R)
8		A [f]	99	94/ 6	96(S)
9		A [g]	95	88/12	90(R)
10		A [h]	55	82/18	77(R)
11		E	79	>94/ 6[l]	93(R)
12		D	61	80/20	88(S)
13	 [d]	A	97	93/ 7	94(R)
14		A	57	>95/ 5[l]	>95(I)

[a] Conditions as in ref 9. [b] Mixture of two isomers (E/Z = 2/98). [c] Mixture of two isomers (E/Z = 4/1). [d] Mixture of two isomers (E/Z = 1/6). [e] A: benzaldehyde. B: pentanal. C: cinnamaldehyde. D: butanal. E: crotonaldehyde. [f] **1b** was used as a ligand. [g] Nitroethane was used as a solvent. [h] Dichloromethane was used as a solvent. [i] The diastereomer ratio was determined by analysis of 500-MHz ^{1}H NMR spectra. [j] The values correspond to the major isomers. [k] Reference 10. [l] Not determined.

and diastereoselectivities was observed in the reactions with saturated aldehydes. It is noteworthy that, regardless of the stereochemistry (E or Z) of starting enol silyl ethers generated from ethyl ketones, erythro aldols were highly selectively obtained in the present reactions.[6] The observed unprecedentedly high erythro selectivities together with their independence of the stereochemistry of silyl ethers in the CAB-catalyzed reactions are fully consistent with Noyori's TMSOTf-catalyzed aldol reactions of acetals and, thus, may reflect the acyclic extended transition state mechanism postulated in the latter reactions (Figure 1).[7] It was of considerable interest to us that the diastereoselectivities of these reactions showed significant solvent dependency; thus, in CH_2Cl_2 (standard solvent for this type of reaction) the ratio dropped to 82/18 (entry 10). The polar solvent should be helpful for the polarized extended transition state model.[8] Judging from the product configurations, CAB catalyst (from natural tartaric acid) should effectively cover the *si* face of carbonyl on its coordination and the selective approach of nucleophiles from the *re* face should result. That behavior is totally systematic and in good agreement with the results of previously reported CAB-catalyzed Diels-Alder reactions.[2] Thus it follows that the sense of asymmetric induction of CAB-catalyzed reactions is the same for all aldehydes examined. Although the enol ethers derived from methyl ketones exhibited modest asymmetric induction (entries 1-4), this reaction would be generally applicable to various ketone silyl ethers and aldehydes.[9] Further studies of the reaction mechanism and the scope of these transformations are in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

(6) The reaction of a silyl ether of *tert*-butyl ethyl ketone (Z form) exceptionally gave the threo adduct predominantly (74/26 ratio). See ref 7.

(7) (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. In the case of the reaction of *tert*-butyl ethyl ketone (R^1 = *t*-Bu, R^2 = Me, Z form, in Figure 1), it could be considered that the steric repulsion between R and R^1 (=*t*-Bu) in the erythro transition state becomes more significant than that between R and R^2 in the threo transition state.

(8) The superiority of propionitrile as a solvent for catalytic asymmetric aldol-type reactions has been reported: see ref 1d.

(9) The following experiment is typical: To a solution of monoacylated tartaric acid **1** (74 mg, 0.2 mmol) in propionitrile (1 mL) was added BH_3·THF (0.12 mL of 1.68 M solution in THF, 0.2 mmol) at 0 °C under Ar. The reaction mixture was stirred for 1 h at that temperature, during which period the evolution of hydrogen gas ceased, and then the solution was cooled to -78 °C. To this were introduced 3-(trimethylsiloxy)-2-pentene (190 mg, 1.2 mmol, E/Z = 4/1) and benzaldehyde (102 μL, 1.0 mmol) successively. After stirring for 2 h, the solution was poured into diluted hydrochloric acid and the product was extracted with ether. The solvent was evaporated, and the residue was treated with 1 N HCl-THF solution (2 mL, 1/1 in vol). Usual workup followed by chromatographic separation gave aldol adducts (185 mg, 96% yield).

(10) (a) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 1441. (b) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513. (c) Muraoka, M.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 337. (d) Enders, D.; Lohray, B. B. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 581. (e) Reference 1b.

Transformation of C-Terminal Serine and Threonine Extended Precursors into C-Terminal α-Amidated Peptides: A Possible Chemical Model for the α-Amidating Action of Pituitary Enzymes

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Received June 22, 1990
Revised Manuscript Received December 4, 1990

The primary amide functionality present at the carboxyl terminus in the majority of polypeptide hormones and in many bioactive neuropeptides[1] is known[2] to be derived from a glycine (Gly) residue at the C-terminus of their Gly extended precursors.[3]

We present here a practical, in vitro model for the terminal amidation reaction using either a serine (Ser) or threonine (Thr)[4]

(1) Mains, R. E.; Eipper, B. A.; Glembotski, C. G.; Dores, R. M. *Trends NeuroSci. (Personal edt.)* **1983**, *6*, 229.

(2) Bradbury, A. F.; Finnie, M. D. A.; Smyth, D. G. *Nature* **1982**, *298*, 686. Eipper, B. A.; Mains, R. E.; Glembotski, C. G. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 5144.

(3) This reaction is catalyzed by the peptidylglycine α-amidating enzyme (PAM). Although not conclusive, it is believed that the process involves α-hydroxylation to carbinolamides, which can be nonenzymatically transformed to terminal amides. The α-hydroxylation can be effected either directly or through an *N*-acylimine. A subsequent "retroaminal" process would result in amide. (For leading references, see: Bradbury, A. F.; Smyth, D. G. *Biosci. Rep.* **1987**, *7*, 907. Eipper, B. A.; Mains, R. E. *Annu. Rev. Physiol.* **1988**, *50*, 333. Bateman, R. C., Jr.; Youngblood, W. W.; Busbuy, W. H., Jr.; Kizer, J. S. *J. Biol. Chem.* **1985**, *260*, 9088. Bradbury, A. F.; Smyth, D. G. *Eur. J. Biochem.* **1987**, *169*, 579. Ramer, S. E.; Cheng, H.; Palcic, M. M.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 8582. Katopodis, A. G.; May, S. W. *Biochemistry* **1990**, *29*, 4541. Reddy, K. V.; Jin, S.-J.; Arora, P. K.; Sfeir, D. S.; Maloney, S. C.; Maloney, F.; Urbach, F. L.; Sayre, L. M. *J. Am. Chem. Soc.* **1990**, *112*, 2332. Young, S. D.; Tamburini, P. P. *J. Am. Chem. Soc.* **1989**, *111*, 1933. Tajima, M.; Iida, T.; Yoshida, S.; Komatsu, K.; Namba, R.; Yanagi, M.; Noguchi, M.; Okamoto, H. *J. Biol. Chem.* **1990**, *265*, 9602.) We are grateful to a referee for bringing to our notice very pertinent recent references.

0002-7863/91/1513-1042$02.50/0

Table I. Cleavage of C-Terminal Serine Peptides to C-Terminal Amides with in Situ Generated RuO_4 at pH 3

X-Pep-Ser-OMe[a] $\xrightarrow{i}$ X-Pep-NH_2

entry	X-Pep-Ser-OMe [mp, °C; $[\alpha]^{30}_D$, deg (*c*, solvent)[b]]	X-Pep-NH_2 [yield, %; mp, °C; $[\alpha]^{30}_D$, deg (*c*, solvent)]
1	Bz-Gly-Ser-OMe [82–4; –2.3 (3.3, MeOH)]	Bz-Gly-NH_2 (54; 170–1)
2	Bz-Ala-Ser-OMe [134–5; +10.8 (0.4, MeOH)]	Bz-Ala-NH_2 [49; 232–4; +21.1 (1.7, MeOH)]
3	Bz-Leu-Ser-OMe [95–7; +24.1 (3.3, MeOH)]	Bz-Leu-NH_2 [68; 169–70; +2.1 (1.6, $CHCl_3$)]
4	Bz-Phe-Ser-OMe [105–6; +2.1 (3.3, MeOH)]	Bz-Phe-NH_2 [79; 183–4; –27.8 (2.8, MeOH)]
5	Bz-Pro-Phe-Ser-OMe [182–4; –112.3 (3.4, $CHCl_3$)]	Bz-Pro-Phe-NH_2 [70; 188–90; –75.2 (2, MeOH)]
6	Boc-Ala-Ala-Ser-OMe [156–8; –24 (0.5, $CHCl_3$)]	Boc-Ala-Ala-NH_2 [78; 145–8; –38.9 (1.7, MeOH)]
7	Bz-Val-Phe-Ser-OMe [165–7; –13.9 (3.3, MeOH)]	Bz-Val-Phe-NH_2 [65, 238–9; –26.8 (0.9, MeOH)]
8	Bz-Glu-(γ-OMe)-Ser-OMe (134–6)	Bz-Glu-(γ-OMe)-NH_2 (90; 136–7)

[a] X = Bz/Boc; Pep = peptide unit; i: $NaIO_4/RuCl_3{\cdot}3H_2O/(CH_3CN/CCl_4$/pH 3 phosphate buffer, 1:1:2, v/v/v)/room temperature/1.5 h. [b] ±0.05°.

Table II. Cleavage of C-Terminal Threonine Peptides to C-Terminal Amides with RuO_4 at pH 3

X-Pep-Thr-OMe[a] $\xrightarrow{i}$ X-Pep-NH_2

entry	X-Pep-Thr-OMe [mp, °C; $[\alpha]^{30}_D$, deg (*c*, solvent)[b]]	X-Pep-NH_2 (yield, %)[c]
9	Bz-Gly-Thr-OMe [138–40; –6.2 (3.3, MeOH)]	Bz-Gly-NH_2 (72)
10	Bz-Ala-Thr-OMe [68–70; +6.1 (3.3, $CHCl_3$)]	Bz-Ala-NH_2 (65)
11	Bz-Leu-Thr-OMe [113–4; –5.4 (3.3, MeOH)]	Bz-Leu-NH_2 (72)
12	Bz-Phe-Thr-OMe (145–6)	Bz-Phe-NH_2 (68)
13	Bz-Gly-Phe-Thr-OMe (157–9)	Bz-Gly-Phe-NH_2 (51)
14	Bz-Val-Phe-Thr-OMe [205–7; –20.9 (2.3, MeOH)]	Bz-Val-Phe-NH_2 (57)
15	Boc-Ala-Ala-Thr-OMe [155–6; –53.9 (3.3, MeOH)]	Boc-Ala-Ala-NH_2 (86)

[a,b] See footnotes for Table I; i: $NaIO_4/RuCl_3{\cdot}3H_2O/(CH_3CN/CCl_4$/pH 3 phosphate buffer, 1:1:2, v/v/v)/room temperature/1.5 h. [c] Excepting in the case of entry 13 giving rise to Bz-Gly-Phe-NH_2 (mp 177–8 °C; $[\alpha]^{30}_D$ = +2.6° (2.6, MeOH)], the melting points and rotations of all other products are reported in Table I.

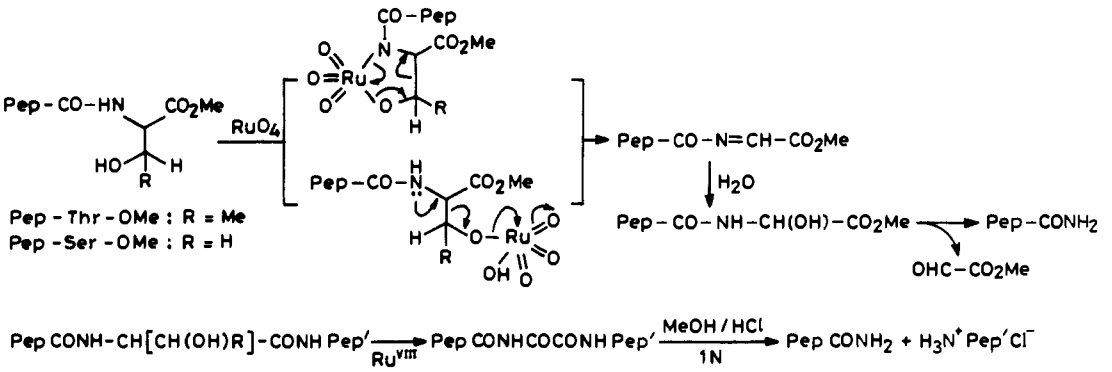
Table III. Oxidation of N-Terminal and Nonterminal Ser/Thr Peptides with RuO_4 at pH 3: Isolation of Oxalamide Derivatives

X-NH-L-CO-Pep-OMe[a] $\xrightarrow{i}$ X-NH-C*O-CO-Pep-OMe

entry	X-NH-L-CO-Pep-OMe [mp, °C; $[\alpha]^{26}_D$, deg (*c*, solvent)]	X-NH-C*O-CO-Pep-OMe[b] [mp, °C; yield, %; $[\alpha]^{28}_D$, deg (*c*, solvent)]
16	Z-Ser-Gly-OMe [79–80; –8.1 (3.3, $CHCl_3$)]	Z-NH-CO-CO-Gly-OMe (132–3; 91)
17	Z-Ser-Ala-OMe [104–6; –7.8 (3.7, $CHCl_3$)]	Z-NH-CO-CO-Ala-OMe (70–1; 66)
18	Z-Ser-Phe-OMe [102–4; –2.7 (3.3, MeOH)]	Z-NH-CO-CO-Phe-OMe [82–3; 82; +32 (3.2, $CHCl_3$)]
19	Z-Ser-Leu-OMe (syrup)	Z-NH-CO-CO-Leu-OMe [syrup; 85; –7.5 (13.5, $CHCl_3$)]
20	Z-Ser-Ser-OMe [136–9; –4.2 (3.3, MeOH)]	Z-NH-CO-CO-NH-CO-CO_2Me (94–6; 16) + Z-NH-CO-CO-NH_2 (199–200; 32)
21	Z-Thr-Gly-OMe [94–7; –12.3 (2.2, MeOH)]	Z-NH-CO-CO-Gly-OMe (132–3; 83)
22	Z-Thr-Ala-OMe [112–4; –28.3 (3.3, MeOH)]	Z-NH-CO-CO-Ala-OMe (70–1; 93)
23	Z-Thr-Phe-OMe [85–7; –2.8 (3.3, MeOH)]	Z-NH-CO-CO-Phe-OMe (83–4; 85)
24	Z-Thr-Leu-OMe (syrup)	Z-NH-CO-CO-Leu-OMe (syrup; 86)
25	Z-Thr-Thr-OMe [98–9; –10.7 (3.6, MeOH)]	Z-NH-CO-CO-NH-CO-CO_2Me (93–5; 18) + Z-NH-CO-CO-NH_2 (198–200; 40)
26	Boc-Thr-Ala-Ala-OMe (127–8)	Boc-NH-CO-CO-Ala-Ala-OMe (170–3; 92)
27	Bz-Leu-Ser-Leu-OMe [87–8; –25.9 (3.3, $CHCl_3$)]	Bz-Leu-NH-CO-CO-Leu-OMe (75–7; 55)
28	Bz-Ala-Thr-Ala-OMe [206–7; –30.9 (3.3, MeOH)]	Bz-Ala-NH-CO-CO-Ala-OMe [140–1; 80; +1.2 (1.6, $CHCl_3$)]

[a] X = Bz/Boc/Z; L = Ser/Thr; i: $NaIO_4/RuCi_3{\cdot}3H_2O/(CH_3CN/CCl_4$/pH 3 phosphate buffer, 1:1:2, v/v/v)/room temperature/1.5 h. [b] C* was originally C^α of Ser/Thr.

Scheme I



residue in place of Gly. Thus, peptides 1–8 (Table I) and 9–15 (Table II),[5] terminating, respectively, in Ser and Thr, on treatment[6] with in situ generated Ru(VIII) at pH 3, at room temperature for 1.5 h, afforded the expected C-terminal amides in

good yields and with chiral retention.[7]

This facile C–N bond rupture of a Ser/Thr residue is rationalized on the basis of fragmentation of a carbinolamide arising from addition of water to the initially formed acylimine,[8] which, in turn, is produced by the oxidative scission of a Ser/Thr C^{α}–side chain bond, involving either a cyclic or an open ruthenium intermediate (Scheme I). The overall process generates a C-terminal amide retaining the Ser/Thr N and releasing the C_2 unit of carbinolamide possibly as glyoxylate.[9]

Peptides 16–28 (Table III)[5] containing a Ser/Thr residue either at the N-terminal or at nonterminal locations under identical[6] conditions afforded, in excellent yields, novel and stable oxalamides.[10] These, resulting from further oxidation of carbinolamides,[11] exhibited a typical, exchangeable singlet at $\delta \sim 9.5$ (^{1}H NMR) and with 1 N MeOH/HCl at room temperature afforded des Ser/Thr amino terminal products as hydrochlorides and C-terminal amides.

The chemical model presented here affords a mild and practical methodology for the preparation of C-terminal amides from C-terminal Ser/Thr extended precursors. Further, the oxalamides derived from N-terminal and nonterminal Ser/Thr peptides constitute an entirely novel class of peptide analogues possessing extended planar bis-peptide regions, the study of whose conformational and reactivity profile would prove interesting.

Acknowledgment. We are most grateful to Professor S. Ranganathan for advice and encouragement and Professors P. Balaram, IISc., Bangalore, India, and D. Balasubramanian and R. Nagaraj, CCMB, Hyderabad, India, for helpful discussions. Financial assistance from the UGC and CSIR is gratefully acknowledged.

Supplementary Material Available: ^{1}H NMR spectra of **1**, **2**, **5**, **6**, **8**, and the products of **1**, **5**, **6**, and **8** (Table I), of **9–11**, **13–15**, and the product of **13** (Table II), and of **16–28**, the products of **16–28**, and D_2O exchange of the products of **16**, **19**, **21–24**, and **27** (Table III), ^{13}C NMR spectra of **16** and **17** (Table III), IR spectra of **1–5**, **7**, **8**, the products of **1–8**, and authentic samples of the products of **1–3** (Table I), of **9**, **11–15**, the product of **13**, and an authentic sample of the product of **13** (Table II), and of **16–23**, **25–27**, and the products of **16–20**, **22**, **24**, and **26–28** (Table III), and mass spectra of the product of **8** (Table I), of **11** and **12** (Table II), and of **16–20** and **28** (Table III) (111 pages). Ordering information is given on any current masthead page.

(4) Selective cleavage of Ser/Thr peptides has been reported either with strong acids or through *N*-acyloxazolidones or involving N → O acyl shift or via dehydroalanines (Shin, K. H.; Sakakibara, S.; Schneider, W.; Hess, G. P. *Biochem. Biophys. Res. Commun.* **1962**, *8*, 288. Kaneko, T.; Takeuchi, I.; Inui, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 974. Kaneko, T.; Kusumoto, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2155. Lavy, D.; Carpenter, F. H. *Biochemistry* **1970**, *9*, 3215. Fontana, A.; Gross, E. In *Practical Protein Chemistry, A Handbook*; Darbre, A., Ed.; Wiley-Interscience: New York, 1986). However, there is no report for the formation of C-terminal amides from Ser/Thr residues via scission of a C^{α}–side chain bond.

(5) All amino acids used were of the L configuration. The peptide substrates were prepared by usual coupling procedures (DCC/HOBT/DMF/CH_2Cl_2). Satisfactory spectral data and elemental analyses were obtained for all peptides reported.

(6) In a typical cleavage procedure, a mixture of the C-terminal Ser/Thr peptide (1 mmol), $NaIO_4$ (18 mmol), $RuCl_3 \cdot 3H_2O$ (2.2 mol %), and MeCN/CCl_4/pH 3 phosphate buffer (4 mL/4 mL/8 mL) was mechanically shaken in a sealed flask at room temperature for 1.5 h, cooled, cautiously opened, and filtered; the residue was washed with hot EtOAc (2 × 10 mL); the combined filtrates were evaporated in vacuo, stirred with saturated $NaHCO_3$ (15 mL), extracted with EtOAc (3 × 20 mL), and dried ($MgSO_4$); and the solvents were removed to yield the crude product amide, which was crystallized from either hot EtOAc or MeOH.

(7) All product C-terminal amides were found to be identical with authentic samples.

(8) Acylimines are known to be highly reactive and spontaneously add water to give carbinolamines (Malassa, I.; Matthies, D. *Liebigs Ann. Chem.* **1986**, *7*, 1133).

(9) All efforts to isolate any glyoxylate-derived fragment failed.

(10) Fully characterized by ^{1}H and ^{13}C NMR, IR, and mass spectra (see supplementary material).

(11) Ser-Ser/Thr-Thr dipeptides, as expected, fragmented by both modes (**20** and **25**, Table III).

A Carbonyl 1,1-Zwitterion Synthon for Ester and Macrolide Synthesis

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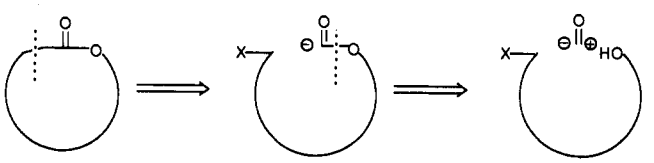
The biological importance of macrolides has led to numerous efforts to develop diverse synthetic entries.[1,4] None of these strategies has invoked the bond disconnection pictured in **1** which naturally leads to the suggestion that an α,ω-disubstituted chain can be linked at the termini if a suitable 1,1-zwitterionic carbonyl synthon exists (i.e., **2**).[5] The efficacy of metal-catalyzed C–C



1 2

bond formation led us to choose a synthon that would be a good partner for such catalysts. Our candidate, chloro(phenylthio)-acetonitrile (**3**), utilizes sulfur because of its desirable electronic properties even though sulfur is frequently thought of as a catalyst poison. In this communication, we record our preliminary successes with this new strategy.

Reagent **3** is available in 75% yield from (phenylthio)acetonitrile[6] by reaction with sulfuryl chloride in carbon tetrachloride[7] at 0 °C. Silver ion assisted chloride substitution may be performed in the alcohol as solvent (Scheme I, example A) or in acetonitrile

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