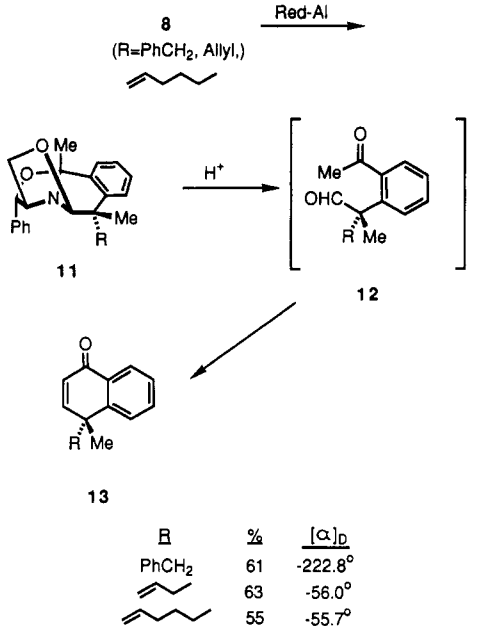
"umbrella" over the ring. It should also be noted that although the nitrogen hybridization in **8** is virtually that of sp^2 (C–N–C angle of 0.1 Å off the plane), nitrogen is known to be highly pyramidalized in amide enolates.[12] Because of this the *N*-lone pair in the amide enolate makes a very good Lewis base (or electron donor).

With reasonable diastereoselectivity achieved using either the dilithiated lactam (for slow reacting alkyl halides) or the zirconated-lithio lactams (for more reactive halides) we proceeded to our goal by reducing the pure dialkylated lactams **8** (Red-Al (Aldrich), toluene, −78 °C, 48 h) to the carbinolamine, which indicated by spectral analysis that it existed as the oxazolidine **11**, presumably formed by intramolecular trapping of the iminium ion by the pendant hydroxy group.[13] The crude material (after ether extraction and concentration) was subjected directly to an ethanolic solution of aqueous 1.0 M $Bu_4NH_2PO_4$ and heated to reflux (48 h).[5] The keto aldehyde **12**, expected to have formed during the hydrolytic removal of the chiral auxiliary, was not observed, and only the desired naphthalenone **13** was isolated. In this fashion, three examples of **13** were formed in ~60% overall yield (from **8**) presumably due to conditions which were proper to effect the aldol cyclization. The products were considered to be optically pure by virtue of the diastereomeric purity of the precursors, **8**.



R	%	$[\alpha]_D$
$PhCH_2$	61	-222.8°
	63	-56.0°
	55	-55.7°

In summary, this preliminary report on our efforts to reach **1** has culminated in an efficient route to chiral, nonracemic, 4,4-dialkylnaphthalenones **13**, which contain the salient stereochemical feature necessary to proceed.

Acknowledgment. Financial support for this study was provided by the National Institutes of Health for which we are grateful.

Supplementary Material Available: Complete X-ray parameters for **8** (R = PhCH) (6 pages). Ordering information is given on any current masthead page.

(12) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. Laube, T.; Dunitz, J. D.; Seebach, D. *Hlev. Chim. Acta* **1985**, *68*, 1373. We have recently determined the X-ray structure of a bicyclic lactam lithio enolate related to those in this paper and also find a high degree of pyramidialization for nitrogen: Lefker, B. A.; Williard, P. G.; Meyers, A. I., unpublished results.

(13) This oxazolidine–iminium ion equilibrium has been noted in other related systems, cf.: Bienz, S.; Busacca, C.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905.

Addition of Zinc Homoenolates to Acetylenic Esters: A Formal [3 + 2] Cycloaddition

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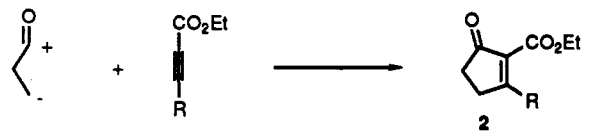
Received April 6, 1990

Summary: Addition of zinc homoenolates to acetylenic esters results in conjugate addition followed by intramolecular acylation of the intermediate allenolate to produce 2-carbalkoxycyclopentenones, formally a [3 + 2] cycloaddition, in a single operation.

Homoenolate reagents have recently proven to be highly versatile reagents in the formation of new carbon–carbon bonds. Methods utilizing homoenolates in acylations, nucleophilic additions, and metal-catalyzed coupling reactions have been reported.[1-3] More recently, conjugate additions of zinc homoenolates in the presence of catalytic copper(I) have been performed on various electrophiles. While Kuwajima and Nakamura[2a,f] and independently

Scheme I



(1) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, *29*, 2395. (c) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, *29*, 3887. (d) Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* **1988**, *29*, 6693. (e) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5791. (f) Chen, H. G.; Hoechstetter, C.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4795. (g) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799. (h) Majid, T.; Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069.

(2) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (b) Oshino, H.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1985**, *50*, 2802. (c) Nakamura, E.; Shimada, J.; Kuwajima, I. *Organometallics* **1985**, *4*, 641. (d) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83. (e) Nakamura, E.; Sekia, K.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 337. (f) Nakamura, E.; Aoki, S.; Sekia, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056.

(3) (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. Tetrahedron *Lett.* **1985**, *26*, 5559. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (c) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157; *Angew. Chem.* **1987**, *99*, 1193.

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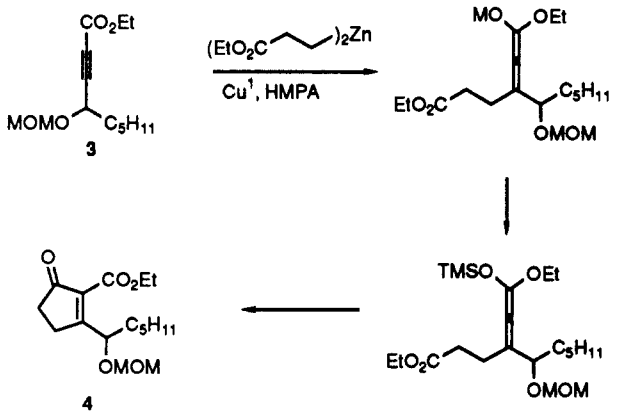
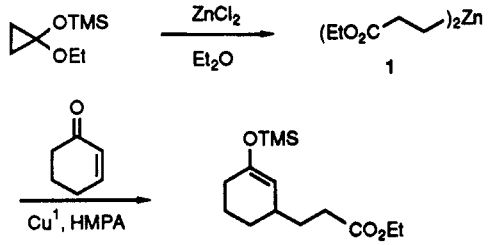
Scheme II



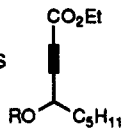
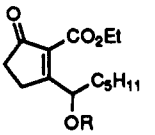
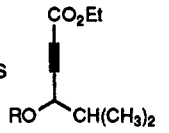
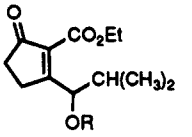
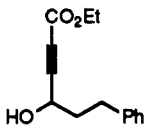
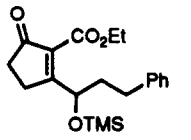
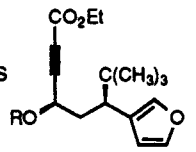
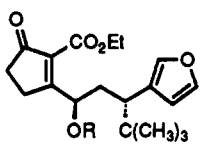
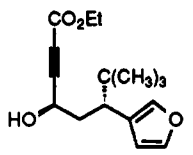
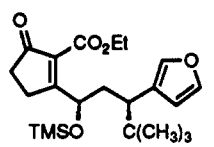
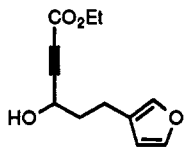
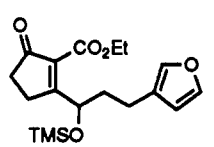
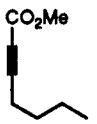
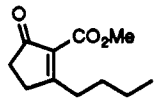
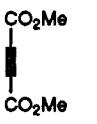
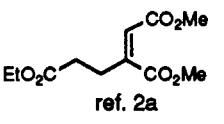
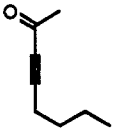
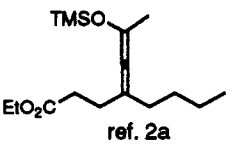
Knochel[1a,g] have reported preparation of silyl enol ethers by the conjugate addition of homoenolate 1 to unsaturated ketones, aldehydes, and esters, no intramolecular capture of the intermediate enolate species has been reported.



Since an ester homoenolate is formally a nucleophile–electrophile tandem, these reagents have the potential for the formation of two carbon–carbon bonds in a single reaction as shown in Scheme I. Based on our earlier studies on the conjugate addition–cycloacylation sequence on acetylenic diesters,[4] we felt that copper-catalyzed conjugate addition of homoenolates to acetylenic esters might provide the corresponding cyclopentenones 2. We report here the first examples of this unique, tandem conjugate addition–cyclization reaction of zinc homoenolates in the preparation of 3-substituted 2-carbethoxycyclopentenones.

Addition of acetylenic ester 3 to a solution of zinc homoenolate 1 in the presence of copper(I), TMSCl, and HMPA provided a 71% yield of the cyclopentenone 4 directly.[5] While the intermediacy of a vinylcopper species cannot be excluded, the reaction most likely proceeds through the allenolate which is trapped as the silyl ketene acetal. This ketene acetal then undergoes intramolecular acylation to produce 4 (Scheme II). The hydroxyl protecting group appears to have little effect on the reaction except when it is electron deficient (entries 2 and 5 in Table I) in which case the yield is somewhat diminished. Also, the free hydroxyl (entries 7, 9–11) can be utilized to give the cyclopentenone with the TMS-protected hydroxyl. Simple alkyl-substituted acetylenic esters (entry 12) also undergo the reaction, although these cases seem to require a minimum of 10 mol % of copper(I). Notably, *no* cyclization is observed in the two cases studied by Nakamura and Kuwajima (entries 13, 14).[2] We believe this to be due to a significant reduction in the nucleophilicity of the intermediate silyl ketene acetal. It is clear that subtle steric and electronic changes can significantly alter the outcome of this process. Studies are underway to evaluate the steric and electronic effects which control this reaction and how they can best be utilized to improve the generality of the process.

Table I

entry	substrate	product	yield
1 R = MOM 2 R = Ac 3 R = H,TMS			71% 50% 70%
4 R = MOM 5 R = Ac 6 R = H,TMS			72% 49% 70%
7			65%
8 R = MOM 9 R = H,TMS			65% 82%
10			83%
11			65%
12			65%
13		 ref. 2a	63%
14		 ref. 2a	73%

In a typical procedure a mixture of 3.75 mL of 1 M zinc chloride in ether and 0.87 g (5 mmol) of [(1-ethoxycyclopropyl)oxy]trimethylsilane in 3.8 mL of ether was stirred for 3 h at 25 °C (2 h under ultrasonic irradiation). The mixture was cooled to 0 °C, and 15 mg (0.07 mmol) of CuBr–Me_2S, 606 mg (2.5 mmol) of acetylenic ester 3, and 0.87 mL (5 mmol) of HMPA were added sequentially. The

(4) Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 3033.

(5) Corey recently reported the addition of dimethyl cyclohexanedicarboxylate dianion to an acetylenic ester to produce a substituted cyclopentenone. This proceeds through 1,2-addition to the ester followed by intramolecular 1,4-addition. See: Corey, E. J.; Su, W. *J. Am. Chem. Soc.* **1987**, *109*, 7534.

mixture was stirred for 2 h at 0 °C and for 4 h at 25 °C and then quenched with saturated ammonium chloride. The mixture was diluted with ether and filtered through Celite. The organic layer was washed with water, dried, concentrated, and flash chromatographed to provide 530 mg (71%) of cyclopentenone 4.

Acknowledgment. We are pleased to thank the National Institutes of Health (GM38904), the Alfred P. Sloan Foundation, the Randleigh Foundation, and Rhone Poulenc, Inc., for generous financial support. We also thank James B. Thomas for technical assistance and helpful discussions.

Lipase-Catalyzed Transesterification in the Synthesis of a New Chiral Unlabeled and Carbon-14 Labeled Serotonin Uptake Inhibitor

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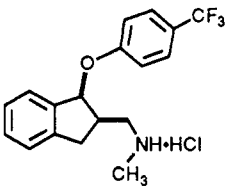
Summary: The synthesis of a new chiral unlabeled and carbon-14 labeled serotonin uptake inhibitor via lipase-catalyzed resolution is described.

The synthesis of chiral drugs is a major challenge in medicinal chemistry[1] since enantiomers may have different biological activities and be responsible for toxic side effects.[2] Currently, there is a widespread consensus that a racemic drug should be considered, not as an individual compound, but as a combination of drugs.[3] However, many synthetic pharmaceuticals are still being developed and marketed as racemates.[4] The development of efficient methods of resolution, asymmetric synthesis,[5] and new chiral analytical techniques[6] will change this situation.

Enzyme-catalyzed kinetic resolution, both in aqueous[7] and nonaqueous[8] media, has emerged as a versatile technique for the synthesis of chiral compounds. Enzymatic catalysis in organic solvents has become increasingly popular among organic chemists[9] and has been found to be especially useful for the synthesis of some unique chiral intermediates and pharmaceuticals.[10]

The indanamine derivative MDL 27777A (1) is a new serotonin uptake inhibitor.[11] Preliminary studies show that (+)-1 (MDL 28618A) is at least 10 times more active in inhibiting serotonin uptake both in vitro and in vivo than (−)-1.[12] The resolution of the racemic alcohol (±)-4

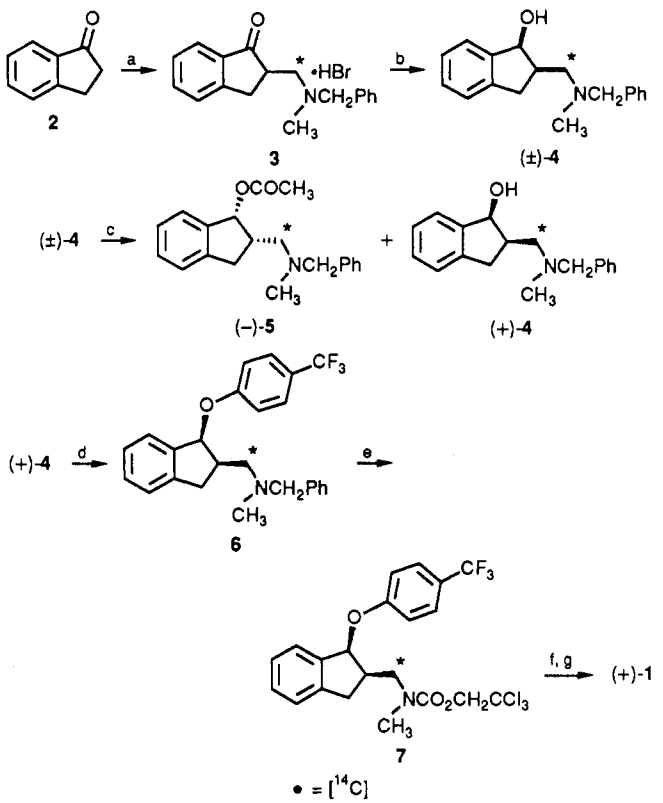


1

via lipase-catalyzed acylation of (−)-4 allowed the synthesis of [^{14}C]-(+)-1, the first example of the application of enzyme-catalyzed reactions in organic solvents for the synthesis of a radiolabeled compound.

Scheme I outlines the synthetic route to (+)-1.[13,14] Paraformaldehyde was condensed in a Mannich reaction with 1-indanone (2) and *N*-benzylmethylamine hydrobromide in refluxing acetonitrile to form 3. Reduction of ketone 3 with L-Selectride (Aldrich) gave alcohol 4 (cis/trans, 20/1); after chromatography, pure 4 was obtained in 88% yield. Lipase from *Pseudomonas fluorescens* (50 mg/mL) was suspended in a solution of alcohol 4 (2.2 g) and vinyl acetate (2.3 equiv) in *tert*-butyl methyl ether (50

Scheme I[a]



[a] (a) [^{14}C]CH_2O, $PhCH_2NHCH_3$·HBr (CH_3CN) reflux, 2 h; (b) 2 equiv of L-Selectride (THF) 0 °C → 22 °C, 16 h; (c) 2 equiv of H_2C=CHOAc, Lipase P (*t*-BuOMe) 22 °C, 4 days; (d) *p*-$FC_6H_4CF_3$, NaH (DMF), 90 °C, 30 min; (e) $ClCO_2CH_2CCl_3$ ($PhCH_3$), reflux, 30 min; (f) Zn (90% HOAc), 23–25 °C, 30 min; (g) HCl(Et_2O).

† Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, OH 45215.

(1) Testa, B.; Mayer, J. M. *Prog. Drug Res.* **1988**, *32*, 249. Smith, R. L.; Caldwell, J. *Trends Pharmacol. Sci.* **1988**, *9*, 75.
(2) Ariens, E. J. *Med. Res. Rev.* **1986**, *6*, 451. Coutts, R. T.; Baker, G. B. *Chirality* **1989**, *1*, 99.
(3) DeCamp, W. H. *Chirality* **1989**, *1*, 2.
(4) Ariens, E. J.; Wuis, E. W.; Veringa, E. J. *Biochem. Pharmacol.* **1988**, *37*, 9.
(5) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1985; Vol. 5. Brown, J. M.; Davies, S. G. *Nature* **1989**, *342*, 631.
(6) *Chiral Separations by HPLC*; Krstulovic, A. M., Ed.; Ellis Norwood Limited: Chichester, 1989.

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