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One-Pot, Four-Different-Component Annulations: Flexible and Efficient Conversion of n-Sized Cycloalkenones into n+4 Alkenolides

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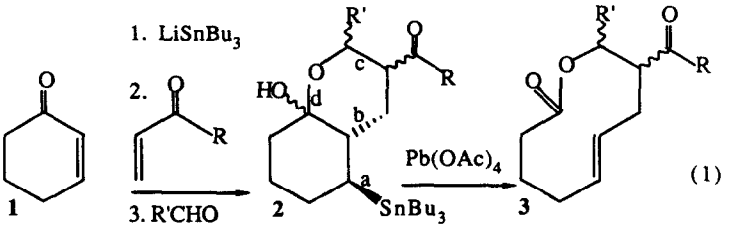
Abstract: Five-, six-, and seven-membered conjugated cycloalkenones undergo one-pot conjugate addition with tri-n-butyltinlithium followed by 1,4-addition to vinyl ketones and then aldol addition to aldehydes leading to cyclic hemiketals 2. Lead tetraacetate oxidative fragmentation produces various 4-atom enlarged, vicinally disubstituted, regiospecifically and stereospecifically unsaturated macrolides 3.

We have recently developed sequential Michael-Michael-Michael ring closure (MIMI-MIRC) reactions as an easy, one-pot procedure forming four new bonds and annulating 6-membered rings via connection of 2+2+2 carbon fragments.[2] This protocol allows ring enlargement of cycloalkenones into the corresponding n+4 cyclic ketones and of alkenolides into the corresponding n+4 cyclic lactones. We report here that cycloalkenones undergo one-pot sequential Michael-Michael-aldol-ring closure (MIMI-ARC) reactions, initiated by tri-n-butyltinlithium,[3] leading to cyclic hemiketals 2 which are oxidatively fragmented by lead tetraacetate[4] to produce efficiently various 4-atom enlarged, vicinally disubstituted (trans and cis), regiospecifically and stereospecifically unsaturated macrolides 3 (eq. 1).[5] These tandem addition reactions were carried out between -65° to -78°C in tetrahydrofuran solvent using slightly more than one equivalent of each successive component; after TLC analysis of a very small aliquot indicated that the first two components had reacted, then the next component was added to the reaction mixture and so on.



(1)

R'	R	% Yield 2	3	3	trans/cis
Me	Et	61.5 x	77 = 47	a	0.7
CH_2=CH	Et	50 x	79 = 39.5	b	2.6
o-BrC_6H_4	Et	67.6 x	70 = 47	c	5.3
o-IC_6H_4	Et	57.5 x	64 = 37	d	2.6
$PhCH_2$	Et	50 x	87 = 43.5	e	1.5
o-$BrC_6H_4CH_2$	Ph	43 x	70 = 30	f	1.0

Several aspects of eq. 1 are noteworthy. Although the six-membered rings of hemiketal intermediates 2 are formed via 2+2+2-annulations and no uncyclized hydroxyketones are detected, this sequence involves a 2-carbon plus 2-carbon plus carbon-oxygen assembly, and therefore the overall transformation depicted in eq. 1 represents cyclic ketone → lactone interconversions; formally, the acyl carbon-vinylic linkage in the reactant cycloalkenone is oxidatively cleaved and in its place is stitched a 3-carbon atom plus 1-oxygen atom spacer group, analogous to the 1-oxygen atom spacer group inserted via Baeyer-Villiger conversion of ketones into esters. In equation 1, the reactant carbon-carbon double bond undergoes inversion of configuration (i.e., cis → trans); macrolides 3 all show a 15-16 Hz coupling constant for the vinylic hydrogen atoms in their 400 MHz ^{1}H NMR spectra. Exclusive formation of such trans-alkenolides is due to the uniquely trans-relationship between bonds a and b in hemiketals 2 and to the concerted anti-elimination during lead tetraacetate-promoted oxidative fragmentation[4] of these γ-hydroxytin intermediates. The stereochemistry of the vicinal substituents ranges between trans:cis ratios of 0.7 - 5.3; attempts to epimerize the acyl side-chain produced only α-enones via β-elimination of the macrolide carboxylate group. The overall yields from simple cyclohexenone to structurally much more complex, chromatographically purified macrolides 3 range from 30-47%. Several of the transformations shown in eq. 1 were performed on gram-scale. Cycloheptenone and cyclopentenone also undergo similar transformations.

To illustrate some of the substantial potential of this four-different-component MIMI-ARC fragmentation sequence, iodophenyl macrolide trans-3d was subjected to iodine-metal exchange[7] and in situ cyclization to produce polyfunctionalized tricyclic indanol[6] 4 in 27% overall yield from cyclohexenone using only three reaction vessels (eq. 2). Likewise, cyclohexenone was converted simply and conveniently into macrolide 5[6]; removal of the phthalimide protecting group,[8] intramolecular cyclization, and aromatization followed by diazomethane esterification produced pure 2,3-disubstituted quinolines 6, R = Et and Ph,[6,9] in 27 and 31% overall yields, respectively, without purification of any of the intermediates leading to final products 6 (eq. 3). Often substituted quinolines are prepared by attaching substituents to a preformed quinoline ring; eq. 3 represents a complementary procedure which constitutes a new quinoline synthesis. The dotted lines in tricycle 4 and in quinoline 6 are meant to indicate the original three structural units which have been combined in these convergent procedures. As a variation on this theme but yet still involving one-pot construction of an intermediate cyclic hemiketal (i.e., 7), eq. 4 represents a short total synthesis of phorocantholide I (8),[5e] a natural 10-membered ring lactone insect secretion, in overall 27.5% from cyclohexenone.

The success of the one-pot, multicomponent annulations shown in equations 1-4 strongly indicates that such a protocol represents a flexible and efficient synthetic method of substantial preparative utility. We are actively exploring further applications.

Acknowledgement

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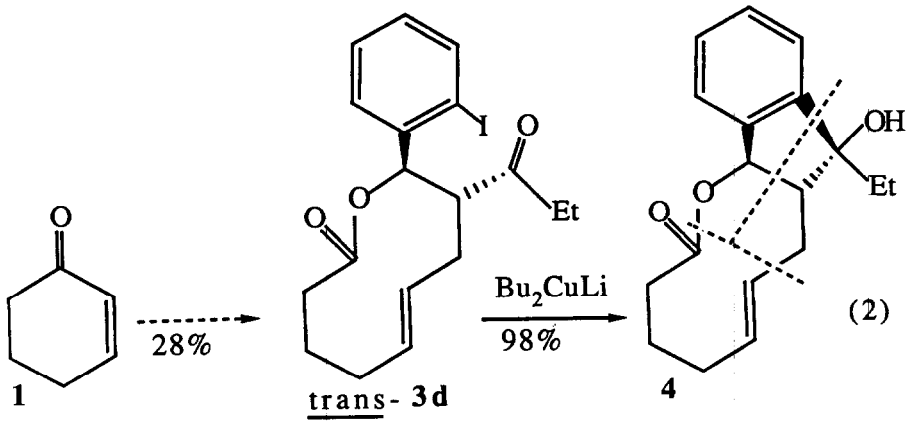
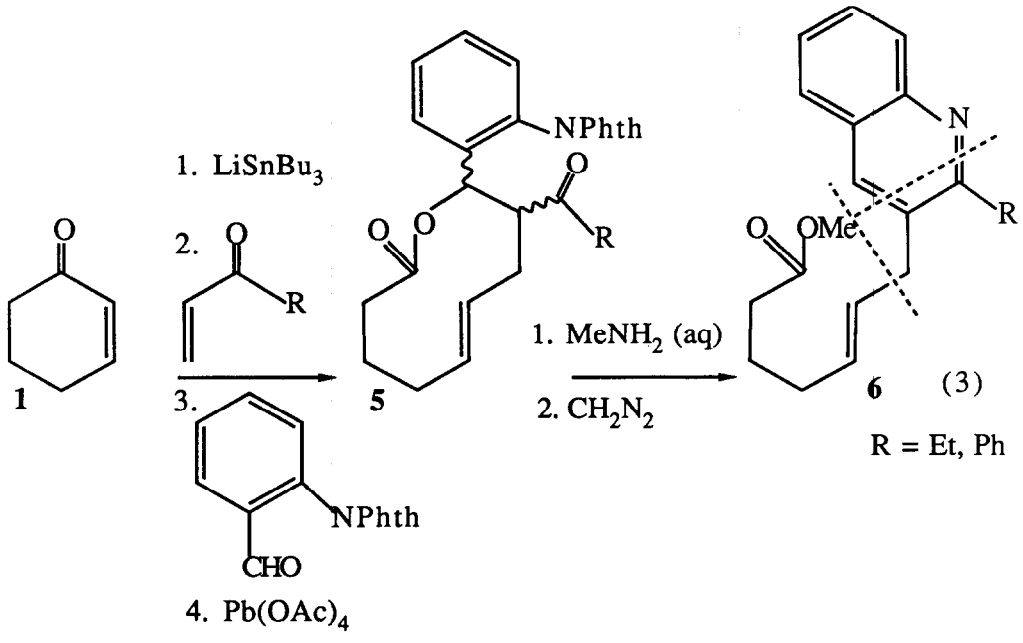
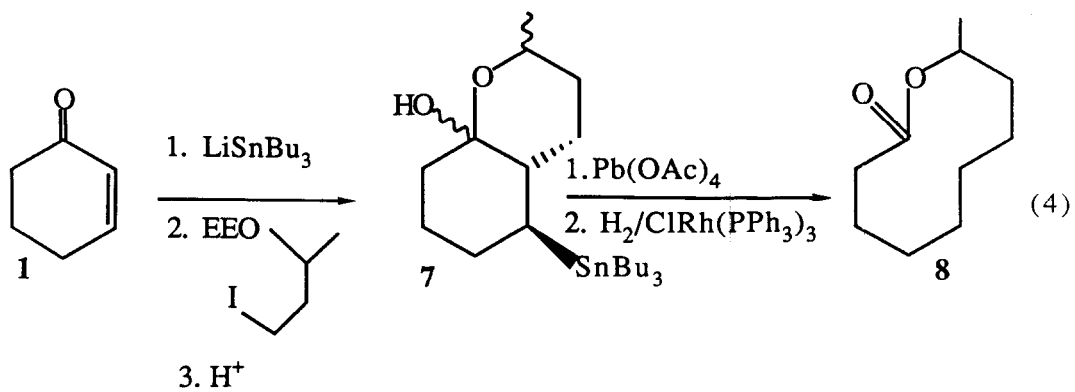

1
28%
trans- 3d
Bu2CuLi
98%
4
(2)


1
1. LiSnBu3
2.
3.
4. Pb(OAc)4
5
1. MeNH2 (aq)
2. CH2N2
6
(3)
R = Et, Ph


1
1. LiSnBu3
2. EEO
3. H+
7
1. Pb(OAc)4
2. H2/ClRh(PPh3)3
8
(4)

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9. The following preparation of quinoline 6, R=Ph, is an illustrative procedure: To tri-n-butyltinlithium (1.80 mmol) in 10 ml of THF at -78°C under an inert atmosphere was added dropwise over 2 minutes 2-cyclohexenone (159 mg, 1.65 mmol) in 2 ml of THF. After 25 minutes at -78°C, phenyl vinyl ketone (247 mg, 1.87 mmol) in 2 ml of THF was added dropwise during 10 minutes. After 1.5 hours, phthalimide protected o-aminobenzaldehyde (533 mg, 2.12 mmol) in 3 ml of THF and 0.5 ml of DMF was added dropwise during 10 minutes. Stirring was continued for 16 hours at -65°C. Saturated aqueous ammonium chloride was added and the reaction mixture was allowed to warm slowly to room temperature. Standard work-up gave a crude intermediate which was dissolved in 5 ml of benzene and added over 5 minutes to a suspension of lead tetraacetate (766 mg, 1.73 mmol) in refluxing benzene. Refluxing for 3.5 hours and standard work-up gave crude macrolide 5, R=Ph, which were dissolved in 6 ml of benzene at 23°C. Methylamine (40% aqueous, 5 ml) was added and stirring was continued at 23°C for 72 hours. After removal of water under reduced pressure, benzene was added and any remaining water was removed azeotropically producing a green oil which was dissolved in 20 ml of chloroform at 0°C. Diazomethane (16.3 mmol) in 250 ml of diethyl ether was added at 0°C. After 20 minutes, glacial acetic acid was added. Standard work-up and column chromatography (1:9 ether:hexane) produced quinoline 6, R=Ph (178.4 mg 31.2%): HRMS m/z calcd. for $C_{23}H_{23}NO_2$: 345.1729. Found: 345.1733; ^1H NMR ($CDCl_3$) δ 7.82 (d, 2H, J = 8 Hz), 8.03 (s, 1H), 8.13 (d, 1H, J = 8.4 Hz), 5.33 (m, 1H, J = 15.2 Hz after decoupling), 5.54 (m, 1H, J = 15.2 Hz after decoupling), 3.66 (s, 3H), 3.48 (d, 2H, J = 6.4 Hz); IR (neat): 960 cm^{-1} (trans double bond).

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