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A CLAISEN REARRANGEMENT STRATEGY FOR THE THREE-ATOM RING EXPANSION OF CYCLIC KETONES. A TOTAL SYNTHESIS OF (±) PRECAPNELLADIENE

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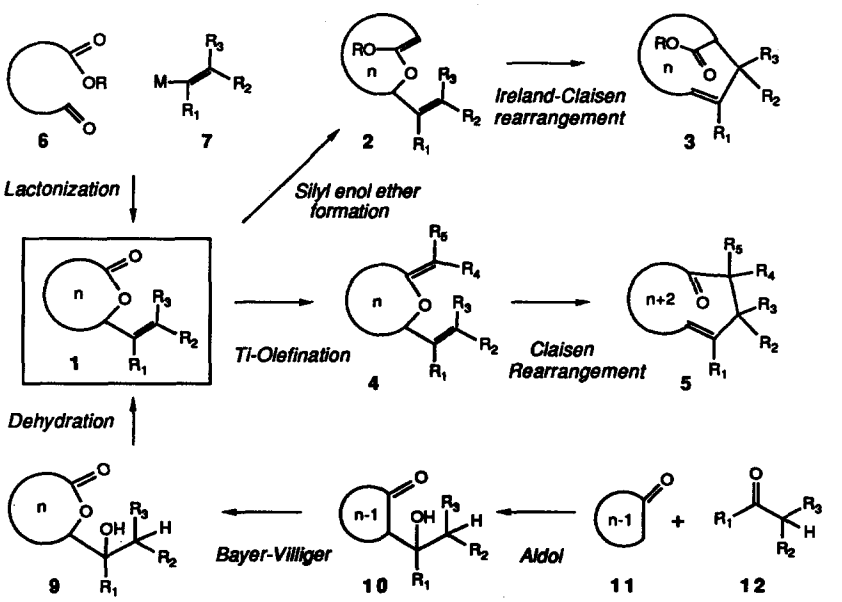
Abstract: The aldol products derived from cyclic ketone enolates undergo Baeyer-Villiger oxidation to give after dehydration the corresponding vinylic-substituted lactones. Titanium-mediated olefination followed by Claisen rearrangement leads to an overall three-atom ring-expansion. The application of this strategy to a concise total synthesis of (±) precapnelladiene (**22**) is reported.

The synthesis of eight-membered ring carbocycles is an area of considerable recent activity. While several novel approaches to these systems have been reported, culminating in a number of elegant natural product syntheses,[1] only a few general and versatile strategies exist as compared to the plethora of efficient methods available for the synthesis of smaller rings.

This paper describes a strategy applicable to the synthesis of eight-membered rings based on the overall three-atom ring-expansion of cyclic ketones via a Claisen rearrangement. The key intermediate is a vinylic-substituted lactone,**1**. This type of compound has been previously used by Danishefsky, Burke and others[2] for the conversion to carbocyclic systems of the same ring size (**3**) via the Ireland-Claisen rearrangement of the corresponding silyl-enol ether, **2**.



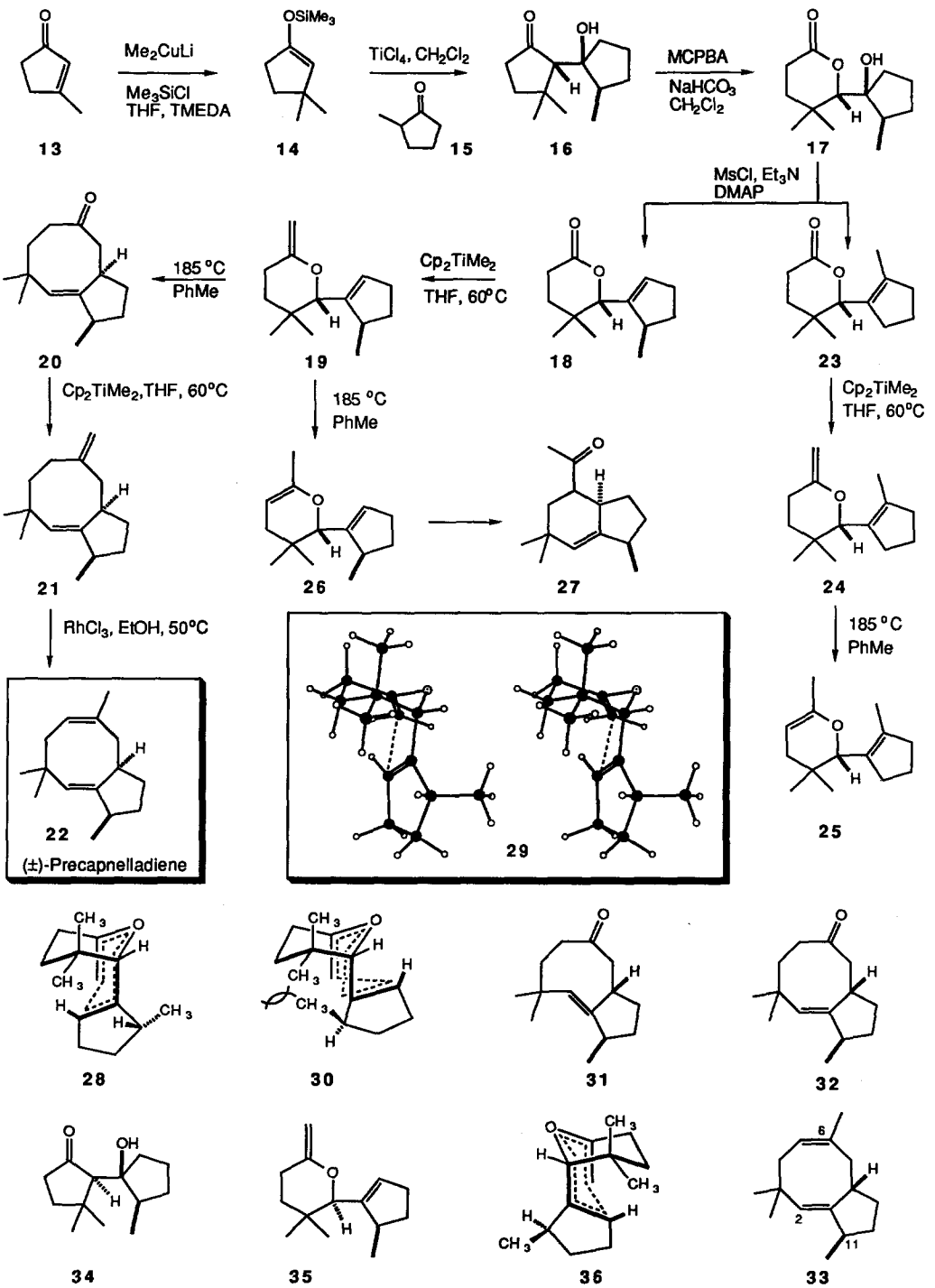
A two-atom ring expansion of **1** is possible via the olefination of the carbonyl to give the enol ether **4**, followed by a Claisen rearrangement to afford the cyclic ketone **5**. Although the powerful transformation of **4** to **5** is relatively unexplored, several examples are known.[3-6] The five to seven ring expansion of this kind (n=5) was first reported by Rhoads.[3,4] Some applications of the analogous six to eight ring expansion (n=6) were reported by Paquette,[5] in a strategy involving the addition of a vinylic organometallic reagent **7** to a dicarbonyl compound **6**, followed by lactonization.

We report herein an alternative approach to the synthesis of compounds of type **1**, which begins with the aldol reaction between cyclic ketone **11** and carbonyl compound **12**. Subsequent Baeyer-Villiger reaction of aldol product **10**, followed by dehydration of hydroxylactone **9** leads to **1**. Overall, this is a convergent strategy employing readily available carbonyl precursors and involving a three-atom ring expansion of **11** to **5**. A key feature of our approach is the utilization of our recently discovered titanium-mediated olefination methodology[7] for the conversion of **1** to **4**.

This ring-expansion strategy has a broad scope and can be employed to the syntheses of a variety of functionalized carbocyclic or polycyclic systems (**5**). Described below is an illustrative application to the synthesis of the cyclooctanoid natural product (±)-precapnelladiene (**22**). This unusual sesquiterpene isolated from a soft coral[8] does not obey the isoprene rule and is considered to be the parent hydrocarbon of a number of polyhydroxy capnellene derivatives.[9]

The synthesis began with conjugate addition of dimethylcuprate to 3-methylcyclopentenone (**13**) in the presence of trimethylsilyl chloride,[10] affording silyl enol ether **14** in 89% yield. Mukaiyama aldol reaction[11] between **14** and (±)-2-methylcyclopentanone (**15**) gave derivative **16**, (93%), which underwent quantitative Baeyer-Villiger oxidation affording only hydroxy-lactone **17**. The subsequent dehydration step presented us with some difficulty, as the desired olefinic lactone **18** was contaminated with the tetrasubstituted olefin derivative **23**. This transformation was best carried out with mesyl chloride, triethylamine and dimethylaminopyridine,[12] affording a quantitative yield of an unseparable 3:2 mixture of **18**:**23**. Methylenation with dimethyl titanocene[7] led to enol ethers **19** and **24** in 90% yield. Thermolysis of this mixture in a sealed tube coated with NaOH, followed by chromatography, produced the desired cyclooctanone **20** (45%, ^{13}C-NMR: 212.5 δ, C=O) and the isomeric 6/5 system **27** (15%). The formation of **27** is a result of partial isomerization[1b] of **19** to **26** followed by an alternative Claisen rearrangement (cf. **2**→**3**). Another product obtained was the enol ether **25** (30%), formed by the isomerization of **24**, suggesting that the tetrasubstituted olefin in **24** or **25** hinders the Claisen rearrangement in these systems. Ketone **20** was methylenated with dimethyl titanocene[7] leading to diene **21** in 92% yield. Isomerization[1a] of **21** with $RhCl_3$ at 50°C produced a 1:1 mixture of **21** and (±)-precapnelladiene (**22**). The ^{1}H- and ^{13}C-NMR data of **22** matched those reported in the literature for the natural product,[1b,1e,8] indicating that the relative stereochemistry of the two stereogenic centers was the desired one and not that of epi-precapnelladiene, **33**.[1a,13]

The Claisen rearrangement of **19** proceeded with high stereoselectivity. Molecular models indicated that the chair-chair transition state **28** (stereoview **29**) should be more favored over the chair-boat transition state **30**. The latter transition state would lead to the unstable *trans*-cyclooctenone **31**, which upon isomerization to **32** would then be converted to **33** rather than **22**.


Me2CuLi
Me3SiCl
THF, TMEDA
TiCl4, CH2Cl2
MCPBA
NaHCO3
CH2Cl2
MsCl, Et3N
DMAP
185 °C
PhMe
Cp2TiMe2
THF, 60°C
Cp2TiMe2,THF, 60°C
185 °C
PhMe
Cp2TiMe2
THF, 60°C
RhCl3, EtOH, 50°C
185 °C
PhMe
13
14
15
16
17
18
19
20
21
22
(±)-Precapnelladiene
23
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36

The observed relative stereochemistry in **22** implies that the aldol reaction among **14** and **15** proceeded with *anti*-selectivity and according to Cram's rule to give **16** with the indicated relative stereochemistry. A *syn*-selectivity in the initial aldol reaction would give **34**, which would lead to the diastereomeric intermediate **35** instead of **19**. Rearrangement of **35** via transition state **36**, which is analogous to **28**, would afford **32** finally leading to **33** instead of the observed **22**.

Overall, the route to **22** reported herein involves only eight steps and is shorter than previous syntheses.[9] The observed diastereoselectivity suggests that this approach may yield the optically active product if enantiomerically pure ketone **15** is used as the starting material.

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13. Major chemical shift differences among **22**[1b] and **33**[1a] : ^{1}H-NMR: 5.02δ (2-H), 1.04δ (11-Me) in **22** vs 4.92δ, 0.99δ in **33**; ^{13}C-NMR: 22.0δ (11-Me), 42.4δ (6-Me) in **22**, vs 19.6δ, 43.8 in **33**.

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