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Natural products synthesis involving anions derived from functionalized mono- and diesters

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Abstract: The reaction path of allyl anion **2**, derived from unsaturated ester **1**, is governed by substituents R^1 - R^4. An understanding of the reaction mechanisms involved has allowed the appropriate design of substrates for specific applications leading to the synthesis of various bioactive natural products.

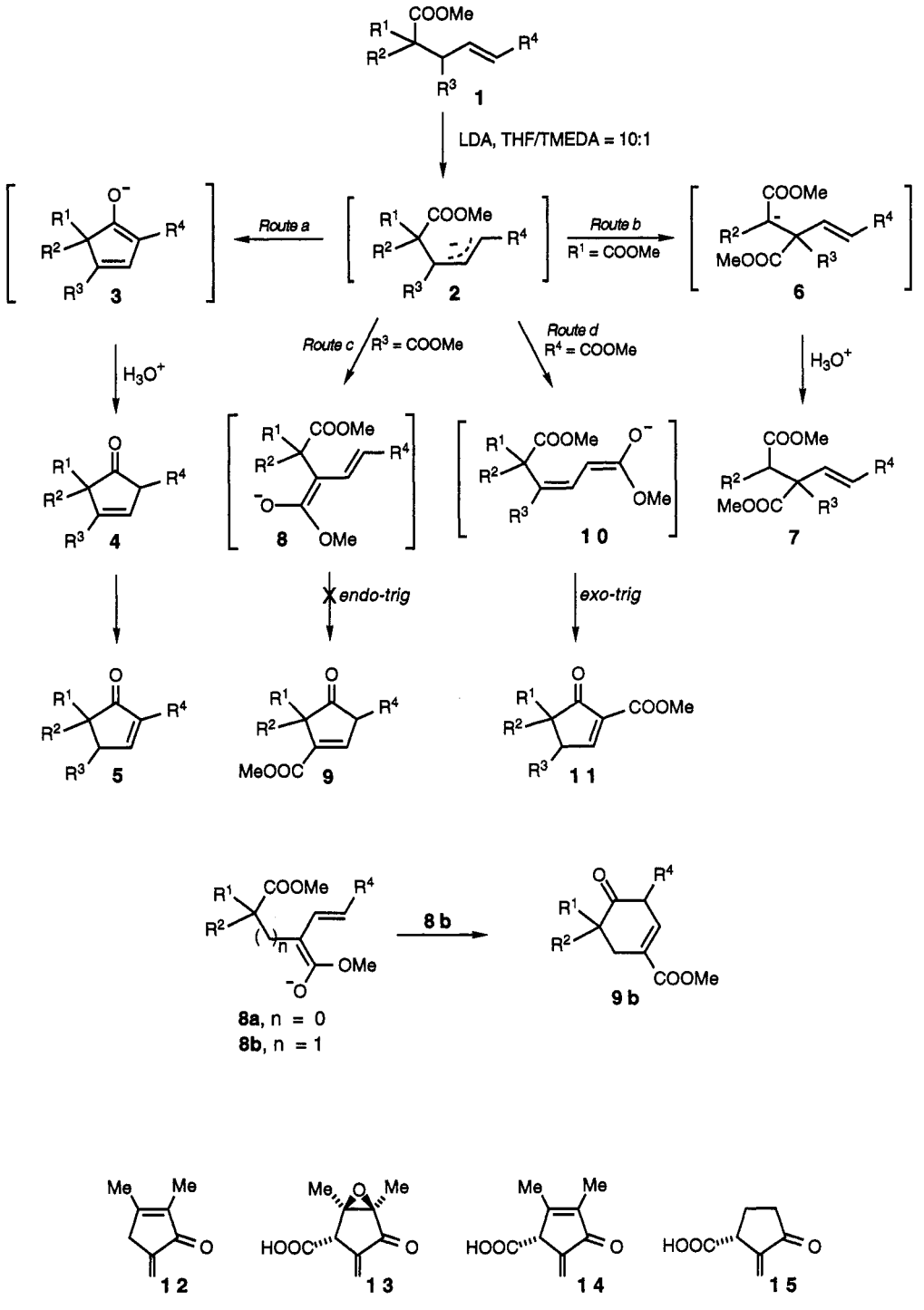
The annulation reaction involving intramolecular acylation of the allyl anion intermediate **2** to give, in the presence of excess base, the dienolate **3** and finally **4** (or its thermodynamically more stable isomer **5**, Scheme 1) has proved to be an efficient method for the preparation of cyclopentenones; yields from such reactions being, in general, high.[1]

In exploring the scope of this cyclization reaction further observations have revealed other competing reaction pathways as summarized below. First, when substituent R^1 is an ester moiety anion **2** takes an alternative path where, instead of cyclization, it undergoes a regiospecific 1,2-acyl migration to give the ester enolate **6,** thence product **7**.[2] Placing the ester group at R^3 also inhibits ring formation as a *5-enolendo-exo-trig* cyclization of the dienolate **8** would be a disfavoured process.[3] However the strain in the transition state for the cyclization of systems such as **8** is diminished in the case of it's homologue, **8b**, which is found to readily cyclize to the 6-membered ring keto ester **9b**.[4] Also as might be expected, placement of the ester group at the terminal of the allyl functionality as shown in **10** (**2**, R^4 = COOMe) facilitates cyclization (*via* a *5-enolexo-exo-trig* process) to provide the enone **11**.[4]

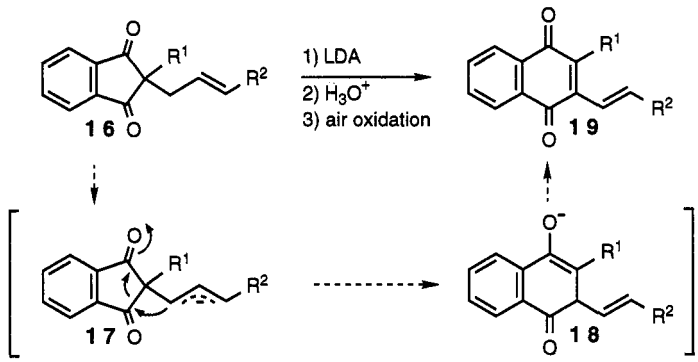
An understanding of the reactions shown above has enabled us to design substrate molecules that can be manipulated to react to yield target bioactive natural products. For example, chemical modification employing host-guest chemistry (by the use of anthracene adducts) coupled with the above annulation reaction has led to the synthesis of labile α-methylene cyclopentenones (*e.g.* **5**, R^1,R^2 = methylene) including naturally occurring cyclopentenoid antibiotics, *viz*: methylenomycin B **12**,[5] methylenomycin A **13** and deepoxy-4,5-didehydromethylenomycin A **14**[6] and sarkomycin **15**.[7]

The synthesis of vinylnaphthoquinone **19** (Scheme 2) was accomplished by taking advantage of the 1,2-acyl migration along the allylic frame-work described above (*route b* in Scheme 1). Here generation of the allyl anion intermediate **17** (by the reaction of corresponding allyl indanedione **16** with LDA in THF/TMEDA) triggered a 1,2-carbonyl migration to give the ring expanded enolate **18**, which, after protonation and subsequent air oxidation during work-up, provided **19**.[2]

Scheme 1

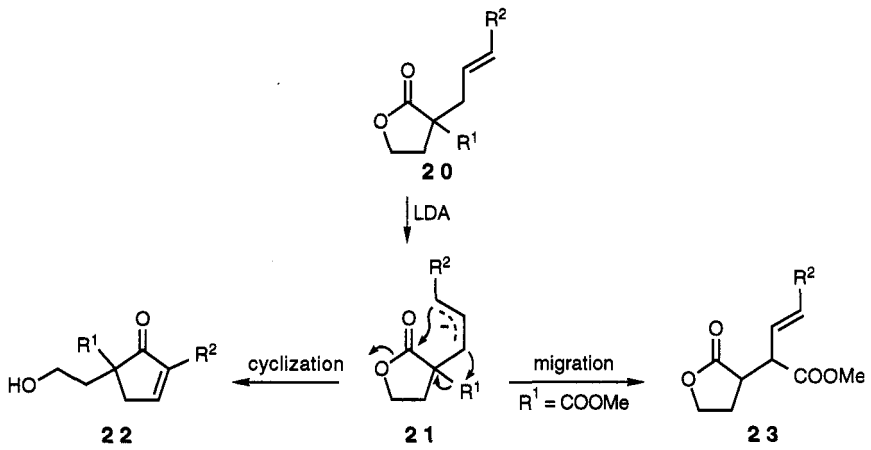

COOMe
R1
R2
R3
R4
1
LDA, THF/TMEDA = 10:1
Route a
Route b
R1 = COOMe
Route c
R3 = COOMe
Route d
R4 = COOMe
H3O+
3
2
6
4
8
OMe
10
7
endo-trig
exo-trig
5
9
11
MeOOC
8a, n = 0
8b, n = 1
8 b
9 b
12
13
14
15
HOOC
Me
O

Scheme 2



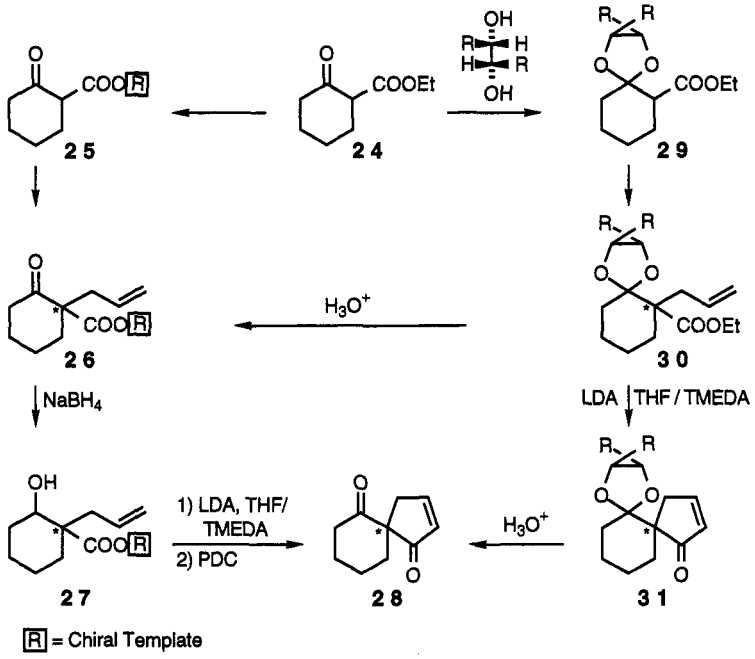
Further study is depicted in Scheme 3 where anion **21,** derived from allyl lactone **20**, is shown to undergo cyclization to give alcohol **22** when R^1 is an alkyl or aryl group. However, when substituent R^1 is an ester moiety (here R^1 = COOMe) only the 1,2- ester migration product **23** is obtained. It is interesting to note that the latter reaction (**21** → **23**) is both completely *regio-* and *acyl specific* with no product resulting from a 1,4- migration of the ester group or from migration of the ester lactone (which would result in ring expansion) being observed.[8]

Scheme 3



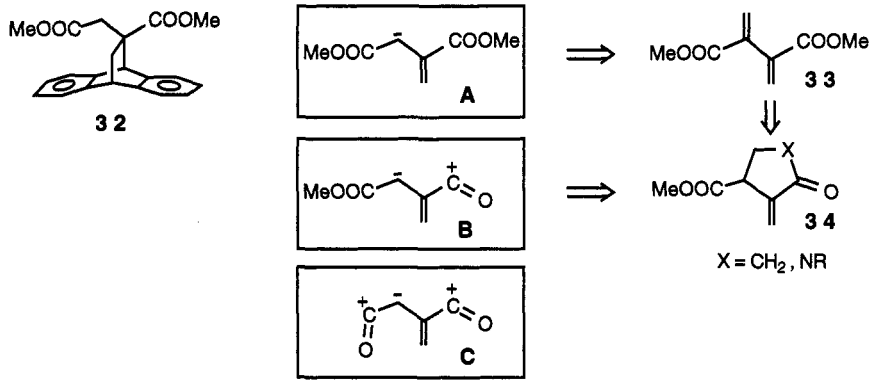
The cyclization reaction involving the allyl anion is also applicable in the enantioselective synthesis of the spiro-diketone **28**, an important intermediate in natural product synthesis. Starting from commercially available ethyl 2-cyclohexanonecarboxylate **24**, enantioselective allylation was accomplished under the influence of a chiral template either *via* **25** or **29** as shown in Scheme 4. Cyclization of **26** was performed by conversion of the keto group to the corresponding alcohol followed by LDA treatment and re-oxidation with PDC to provide the desired spiro-diketone **28**. On the other hand, the acetal **30** could be subjected to cyclization to give **31** and finally **28**, or converted to the corresponding keto allyl ester (*e.g.* **26**) to be manoeuvred along the foregoing reaction pathway just described.[9]

Scheme 4



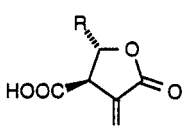
The success of the methyl acrylate - anthracene adduct in the synthesis of α-methylene cyclopentenone antibiotics (**12** - **15**) prompted an investigation of the masked itaconate adduct **32**. Here, it was reckoned that **32**, already known and easily prepared in very high yield from dimethyl itaconate and anthracene,[10] should act as the perfect synthetic equivalents **A**, **B** and **C** shown in Scheme 5.

Scheme 5

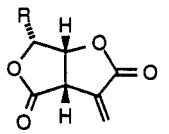


True to expectation adduct **32** has since proved its worth in organic synthesis. For example, the sought-after electron deficient diene **33** and the α-methylene cyclopentanone (**34**, X = CH_2) and lactam (**34**, X = NR) were all easily prepared from adduct **32**. In fact, the syntheses of diene **33**[11] and sarkomycin **15**[7] from **32** are arguably among the most efficient methods reported to date.

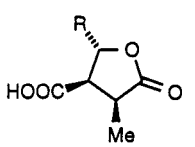
The use of adduct **32** as **B** and **C** synthetic equivalents also appeared quite attractive due to it's anticipated synthetic versatility. Close examination revealed that the functionalities of type **B** and **C** are quite suitable for the assembly of various bioactive methylene lactones and bilactones that have been isolated from microorganisms, *e.g.* methylenolactocin **35a**,[12] protolichesterinic acid **35b**,[13] canadensolide **36a**,[14] and sporothriolide **36b**.[15] Moreover, certain lichen components such as nephrosteranic and roccellaric acids, **37a**[16] and **37b**[17] respectively, also looked amenable to preparation from adduct **32** without much apparent difficulty.



35 a, R = C_5H_{11} Methylenolactocin
b, R = $C_{13}H_{27}$ Protolichesterinic acid



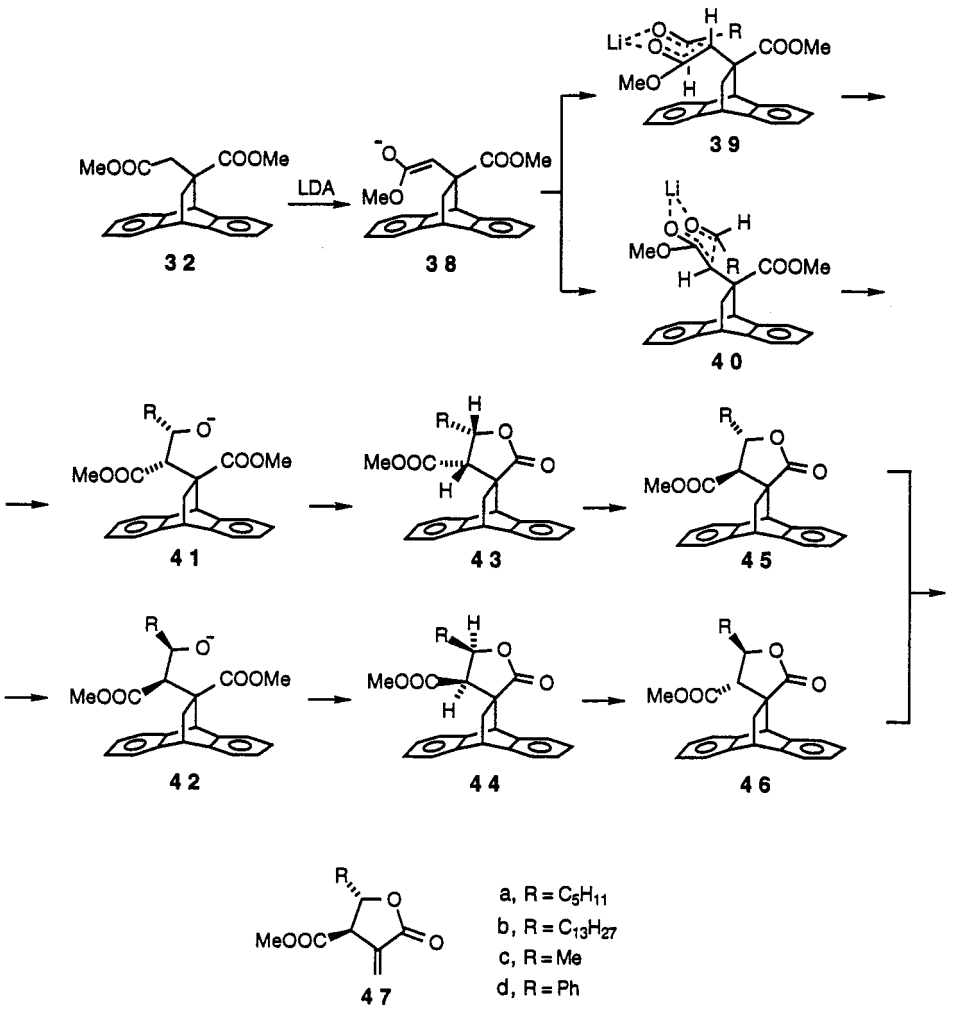
36 a, R = C_4H_9 Canadensolide
b, R = C_8H_{13} Sporothriolide



37 a, R = $C_{11}H_{23}$ Nephrosteranic acid
b, R = $C_{13}H_{27}$ Roccellaric acid

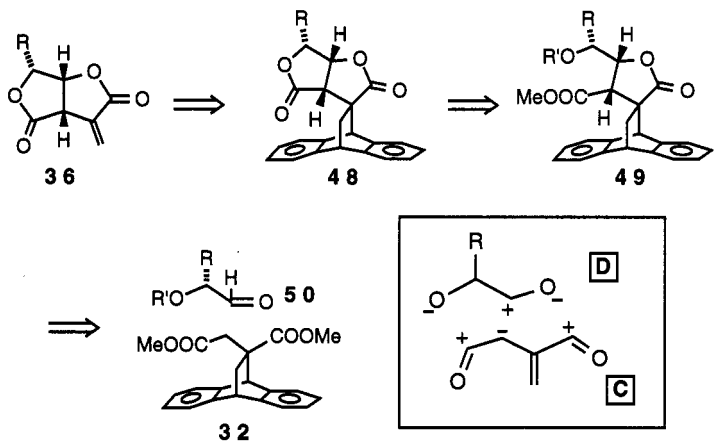
The synthesis of the α-methylene lactones **47a** and **47b** (methyl esters of **35a** and **35b** respectively) was accomplished in a straightforward manner by treating the ester enolate **38**, derived from adduct **32**, with the corresponding aldehydes which resulted in two major products, **43** and **44**, being formed in almost equal amounts. The *cis*- stereochemical relationship between substituents R and -COOMe in both products was determined by their nmr absorptions which included data from NOE experiments. This stereochemical outcome can be explained in terms of the two chair-like transition states shown in **39** and **40**, in which all large substituents occupy equatorial positions (Scheme 6).[18] Equilibration of the spiro-lactones (MeONa / MeOH, r.t.) followed by flash vacuum pyrolysis (of either pure samples or a mixture of **45** and **46**) yielded the racemic methylene lactone **47**.

Scheme 6



It turns out that the chair-like transition states of the aldol condensation of ester enolate **38** which control the *cis*- relative stereochemistry between groups R and -COOMe in the products **43** and **44** are, in fact, ideally suited for the synthesis of canadensolide and sporothriolide, **36a** and **36b** respectively. According to this constraint, a condensation between the adduct **32** with an aldehyde, *e.g.* **50**, would provide the *cis*-substituted lactone **49** which upon deprotection of the alcoholic function would lactonize to give the bilactone **48**, hence **36**. It should be noted that adduct **32** and aldehyde **50** are functioning here as synthetic equivalents of the type **C** and **D** respectively (Scheme 7).

Scheme 7



A synthesis of canadensolide and epi-canadensolide in this manner (method in Scheme 7) has been achieved, and represents an efficient alternative methodology for the synthesis of the bilactone skeleton such as **36**.

To conclude: The research described above has enabled us to fully understand the mechanisms of the cyclization reaction involving the allyl anion intermediate, which has led to its consequent utilization in organic synthesis. Applications of the reaction using functionalized ester adducts, in particular the adduct **32**, has resulted in a good number of synthesis of various bioactive natural products.

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