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Synthesis of Alkyl Citrates (−)-CJ-13,981, (−)-CJ-13,982, and (−)-L-731,120 via a Cyclobutene Diester

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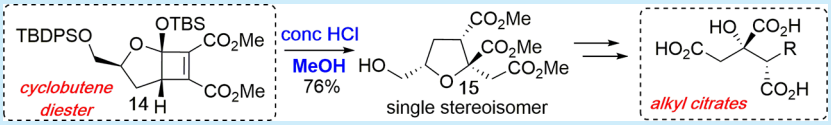
Supporting Information



ABSTRACT: An efficient and step-economic new approach to alkyl citrate natural products from a cyclobutene diester is presented. The key sequence involves a formal [2 + 2]-cycloaddition of a silylketene acetal with dimethylacetylene dicarboxylate to provide the cyclobutene diester **14** with 4.5:1 stereoselectivity. Exposure of diester **14** in acidic methanol effected a hydrolysis, intramolecular oxy-Michael reaction, and cyclobutanone methanolysis cascade to give the triester **15**. Iodination and elimination then afforded a key alkyl citrate alkene intermediate, which was converted into the natural products (−)-CJ-13,982 (**1**), (−)-CJ-13,981 (**2**), and (−)-L-731,120 (**3**) via a cross-metathesis and subsequent reduction.

Alkyl citrate natural products comprise a large family of fungal metabolites that possess a common 2-substituted citric acid moiety. Alkyl citrates such as CJ-13,982 (**1**), CJ-13,981 (**2**),[1] and L-731,120 (**3**)[2] have a basic alkyl-substituted citrate moiety, while the more complex zaragozic acid A (**4**)[3] incorporates the citrate into a highly oxidized 2,8-dioxabicyclo[3.2.1]octane core. Indeed, it recently has been demonstrated that L-731,120 (**3**) is the biosynthetic precursor to zaragozic acid A (**4**) (Figure 1).[4] This suggests that the stereochemistry at C12 in **3** is *R* as shown.

The oxygen atoms at C2, C4, C5 C6, C7, and C11 in zaragozic acid A (**4**) are derived from atmospheric oxygen by an amazing sequence of C−H oxidations.[5] Cyclization by intramolecular ketalization then forms the bicyclic core of **4**. Perhaps even more remarkable is the fact that compound **3** itself is produced as a single enantiomer by only three enzymes,

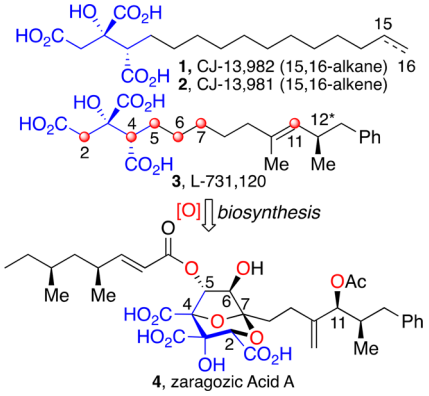


Figure 1. Examples of alkyl citrate natural products.

a HRPKS, citrate synthase, and a hydrolase.[4] Many of the alkyl citrates possess potent activity against squalene synthase (SqS), the enzyme responsible for the first pathway-specific step in the biosynthesis of cholesterol.[6] The most active are the zaragozic acids or sqaulestatins,[5] with zaragozic acid A (**4**) having a IC_{50} = 0.29 nM against rat SqS. Compounds **1**, **2**, and **3** are somewhat less active but still reasonably potent with IC_{50} values of 1.1, 2.8, and 0.77 μM respectively.[1,2]

Alkyl citrates are challenging synthetic targets owing to their high oxidation state and two contiguous stereocenters,[7] and previous syntheses of both natural (−)-**1** and unnatural (+)-**1** and (+)-**2** are summarized in Figure 2. The first syntheses of

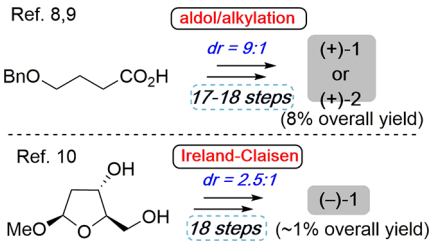


Figure 2. Previous approaches to (+)-**1** and (−)-**1**.

the unnatural enantiomers of CJ-13,982 and CJ-13,981 were reported by Barrett and co-workers,[8] which confirmed the absolute stereochemistry of these compounds. This utilized an aldol/alkylation sequence[9] to construct the contiguous asymmetric centers with good stereocontrol. We have reported the synthesis of natural (−)-CJ-13,982 (**1**) which utilized an

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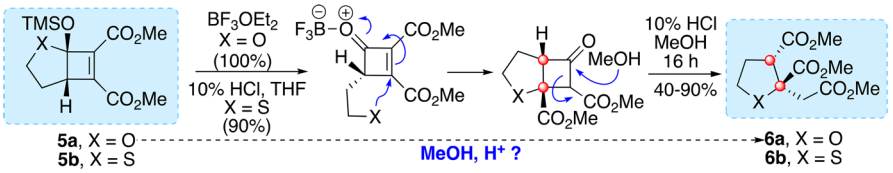
Scheme 1. Rearrangement of Cyclobutene Diesters

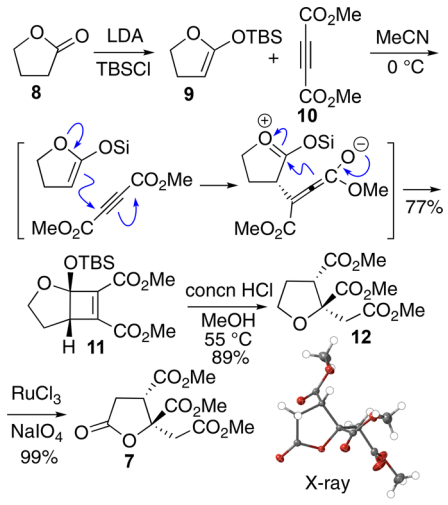


Ireland−Claisen rearrangement as the key step to introduce the two asymmetric centers with some degree of stereocontrol but in low overall yield (Figure 2).[10] The synthesis of the proposed stereoisomer of L-731,120 (**3**) has not been reported. These approaches to simple alkyl citrates are lengthy due multiple functional group transformations. We now report a shorter, highly stereoselective approach to alkyl citrates from cyclobutene diesters, which can be adapted to produce a number of the alkyl citrate family of natural products.

The cyclobutene approach to the citrate moiety is based on studies by Meisch and Wendling,[11,12] who reported that bicyclic cyclobutene diesters of general structure **5** are converted into cyclobutanones upon treatment with $BF_3{\cdot}OEt_2$ (X = O) or aq HCl (X = S) via an unprecedented rearrangement involving acetal cleavage and intramolecular oxa- or thia-Michael addition as shown in Scheme 1. Subsequent acid-mediated cyclobutanone methanolysis[13] afforded the triesters **6** with the relative configuration shown, which maps onto the alkyl citrate moiety. Given this precedent, we postulated that the direct rearrangement of tetrahydrofuran cyclobutenediester **5a** to tetrahydrofuran **6a** might simply be achieved by treatment of **5a** with acidic methanol. This would serve as a rapid entry into the alkyl citrate moiety with the correct stereochemistry and oxidation level.

Our investigations began with the synthesis of the triester lactone **7** as shown in Scheme 2. Cyclobutenediesters can be

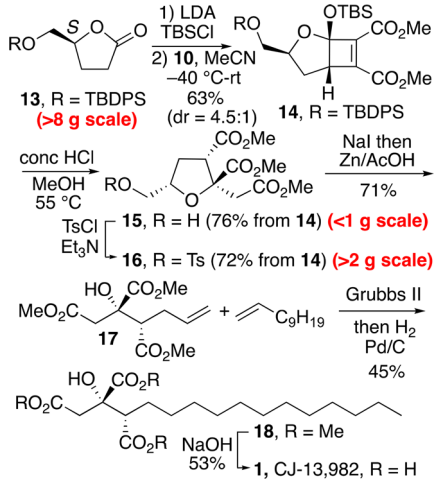
Scheme 2. Model Study



readily accessed via the formal [2 + 2]-cycloaddition of ketene acetals with acetylenic diesters.[14] Dimethyl acetylenedicarboxylate (DMAD) (**10**) reacts with alkyl[14,15] and silyl ketene acetals in the absence of Lewis acid and solvent[11,12] to produce cyclobutene diesters. In our hands, the cyclobutenes produced from TMS ketene acetals proved too labile, so we elected to utilize the TBS ketene acetal.[16] Enolization and silylation of γ-butyrolactone **8** afforded the crude ketene acetal **9**, which was immediately treated with DMAD (**10**) in MeCN to afford the cyclobutene diester **11** as a stable adduct in good yield. Acetonitrile proved to be the best solvent for this formal [2 + 2]-cycloaddition, which presumably proceeds via the mechanism shown, and it is noteworthy that this reaction proceeded efficiently in a solvent *without Lewis acid catalysis*. The cycloaddition also proceeded well in dichloromethane, but other solvents such as THF gave no improvement. Conducting the reaction neat was also inferior, while addition of Lewis acids (e.g., $ZrCl_4$, $TiCl_4$, and $Cu(OTf)_2$) mostly resulted in decomposition of the silyl ketene acetal. In addition, the cycloaddition also proceeded in the presence of hindered base (2,6-di-*tert*-butyl-4-methylpyridine), which demonstrates that traces of acid are not required for this reaction. As hoped, treatment of cyclobutenediester with concentrated HCl in MeOH at 55 °C caused the desired cascade of reactions to afford the tetrahydrofuran **12**[12] as a single diastereoisomer in excellent yield. Oxidation of **12** by treatment with $RuCl_3$ and $NaIO_4$[17] afforded lactone **7** as a crystalline solid, and the stereochemistry was then confirmed by a single-crystal X-ray structure.

Guided by this efficient route to the racemic lactone **7**, we next embarked on an enantiospecific synthesis of (−)-CJ-13,982 (**1**) (Scheme 3). The known optically pure lactone **13**[18]

Scheme 3. Synthesis of (−)-CJ-13,982



(prepared from (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone) was converted into the silyl ketene acetal, and cycloaddition with DMAD (**10**) at −40 °C to rt afforded the major adduct cyclobutene **14** in 63% yield (+ 14% minor diastereoisomer, dr 4.5:1) as a result of the approach of **10** from the least hindered face of the ketene acetal. The isomers were separated by flash chromatography, and the stereochemistry of the major adduct was confirmed by its subsequent conversion into (−)-CJ-13,982 (**1**). Exposure of the cyclobutene to HCl in MeOH at 55 °C induced concomitant silyl ether and acetal hydrolysis,

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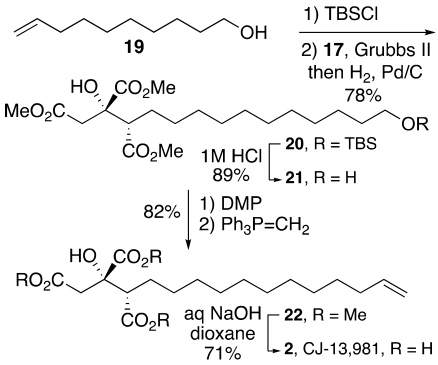
subsequent oxy-Michael addition, and cyclobutene methanolysis to afford the triester **15** as a single stereoisomer good yield. Higher yields were obtained for smaller scale reactions (76% for <1 g); however, for larger scales (>2g), immediate tosylation of the crude alcohol **15** and purification gave tosylate **16** in a better reproducible yield over the two steps. Displacement gave a sensitive iodide, which upon immediate zinc-mediated reductive elimination gave the key alkyl citrate fragment **17**. Cross metathesis (CM) with undecene followed by hydrogenation afforded (−)-CJ-13,982 trimethyl ester **18**. This compound compared well with that reported by us[10] and by Barrett (except for the sign of rotation).[8]

Base hydrolysis of trimethyl ester **18** as previously described[8] (excess aq NaOH, overnight) resulted in considerable decomposition, presumably via a retro aldol pathway.[19] After some experimentation, we found that the use of 5 equiv of 1 M aqueous NaOH in dioxane cosolvent at 80 °C for only 2 h gave (−)-CJ-13,982 (**1**) which could be purified by RP-HPLC. This sequence constitutes the shortest enantiospecific synthesis of this compound.

The synthesis of congener (−)-CJ-13,981 (**2**) is shown in Scheme 4 and begins with alcohol **19**. Silylation followed by

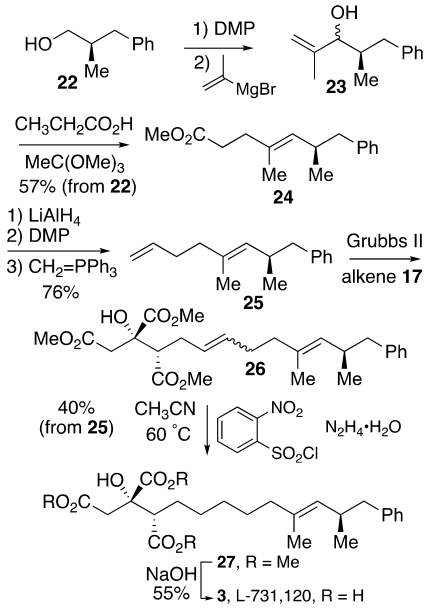
Scheme 4. Synthesis of (−)-CJ-13,981



CM with alkene **16** and hydrogenation afforded triester **20** in good yield. CM using the free alcohol **19** was not as efficient. Desilylation and subsequent methylenation gave the trimethyl ester of CJ-13,981 (**22**), which was also identical to that reported apart from the sign of rotation.[8] Base hydrolysis and RP-HPLC purification gave CJ-13,982 (**2**), the data for which was identical to the natural material.[1]

The synthesis of the zaragozic acid precursor L-731,120 (**3**) is shown in Scheme 5. This began with the known (*R*)-alcohol **22**, secured via Evans' alkylation,[20] which was oxidized to the aldehyde and Grignard addition afforded the alcohol **23** as a mixture of diastereoisomers. Immediate subjection of this to a Johnson−Claisen rearrangement gave ester **24** in 57% overall yield. Reduction, oxidation, and Wittig extension provided the diene **25** and CM with the citrate fragment **16** gave the diene **26** as an *E*/*Z* mixture. Selective reduction of the disubstituted alkene proved challenging with many conditions (e.g., Pd−C/H_2, Wilkinson's catalyst/H_2, cat. $RuCl_3$/$NaBH_4$[21]) failing to give acceptable selectivity for reduction of the disubstituted alkene. Eventually, we found that modified diimide reduction[22] afforded (−)-L-731,120 trimethyl ester **27** along with a small amount of over-reduced byproduct, which were separated using $AgNO_3$-impregnated[23] silica gel. Base hydrolysis under the conditions as described above followed by RP-HPLC purification gave L-731,120 (**3**).

Scheme 5. Synthesis of (−)-L-731,120



In conclusion, we have achieved a new and efficient enantiospecific synthesis of the alkyl citrates CJ-13,982 (**1**) (10 steps from (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone, 7% overall) and CJ-13,981 (**2**) (13 steps, 12% overall) and the first total synthesis of the zaragozic acid biosynthetic precursor L-731,120 (**3**) (10 steps, 7% overall). Noteworthy features of this approach include the construction of the two contiguous asymmetric centers of the citrate by an acid-mediated rearrangement of a cyclobutenediester with complete control of the relative stereochemistry and no need for any functional group manipulations to achieve the triacid oxidation level. This allowed for the synthesis of the key alkyl citrate alkene **17** intermediate in seven steps from a commercially available starting material (30% overall, three chromatographic purifications). The synthesis of higher oxidized more complex alkyl citrates using this methodology is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01665.

Experimental procedures and copies of NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 1837642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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