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Tetrahedron 62 (2006) 5791–5802
Tetrahedron

Exploration of conjugate addition routes to advanced tricyclic components of mangicol A

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Received 22 January 2006; revised 10 March 2006; accepted 21 March 2006
Available online 2 May 2006

Abstract—Two synthetic approaches to the cytotoxic marine natural product known as mangicol A are described. The starting material common to both pathways is the cyclopentenonecarboxylate **11**. The first tactic involves the 1,4-addition to **11** of the cuprate derivable from iodide **10**, while the second proceeds via base-promoted conjugate addition of the regiospecifically generated enolate anion of **41**. The first strategy proceeds by a series of efficient steps to tricyclic aldol **21** and subsequently to β-diketone **7**. The latter proved to be totally unresponsive to schemes aimed at introduction of a butenyl group. The second approach involves earlier introduction of this substituent as realized in stereocontrolled fashion via transition state **42**. While further passage to **44** proved uneventful, this advanced intermediate and analogs thereof proved remarkably recalcitrant to cyclization in the precedented fashion. In no instance was generation of a suitable product realized. These studies serve to underscore the extent to which steric considerations can complicate matters and the extent to which they must be skirted. Finally, a direct enantioselective route to the side chain aldehyde **2** is detailed.
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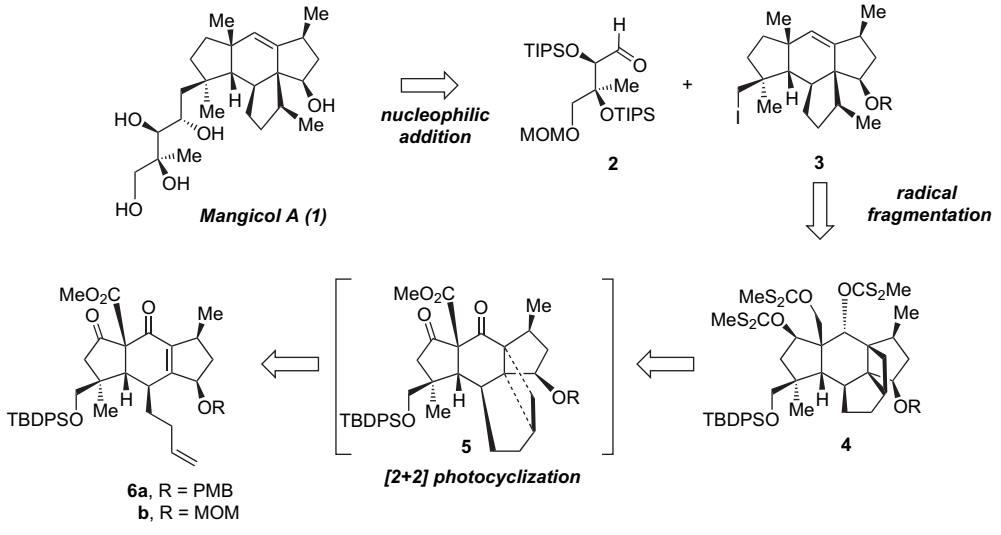
1. Introduction

In a preceding paper,[1] we reviewed background issues concerning the antiinflammatory agent mangicol A (**1**)[2] and reported on the possible application of intramolecular [4+2] cycloaddition strategies for assembly of its central core.[3] In the light of these early results, the decision was made to evaluate alternative routes to **1** that feature convergent Michael reactions as the mode of structural assembly. As outlined in Scheme 1, the retrosynthesis is keyed to the availability of enedione **6** whose role is ultimately to enter into intramolecular photochemical [2+2] cyclization and



Scheme 1.

Keywords: Mangicols; Conjugate additions; Aldol reactions; Functionalized diquinanes; Steric constraints.
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doi:10.1016/j.tet.2006.03.066

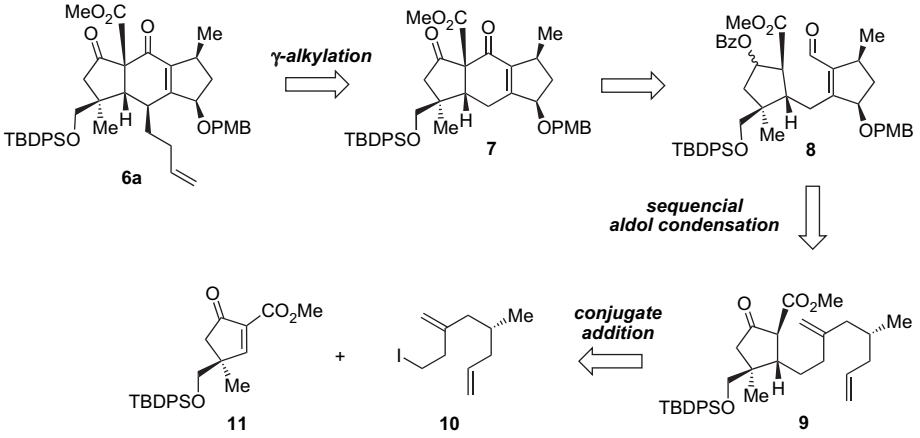
deliver **4**. Presently, the focus of our attention is the need to develop a workable route to **6**. Two subsequences aimed at exploiting conjugate addition pathways to this enedione form the subject of the present account. Also documented is a brief synthesis of the enantiomerically enriched aldehyde **2**.

2. Exploration of a cuprate-based approach

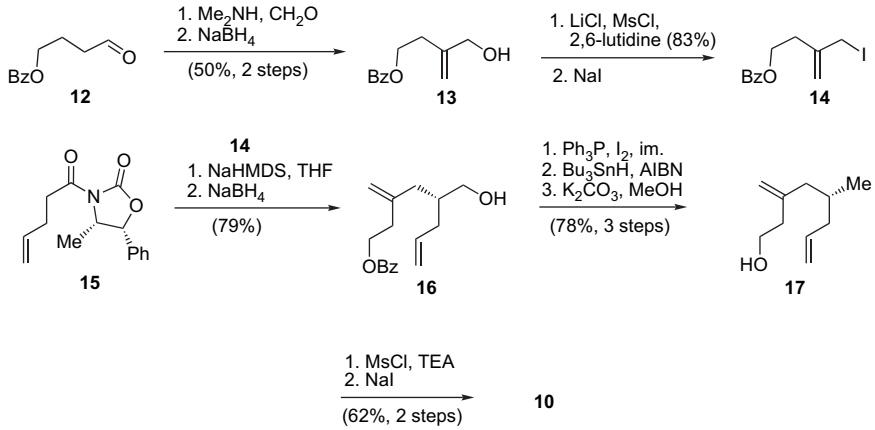
The first option to be explored for ultimately reaching **6a** was based on the suitability of engaging dienyl iodide **10** in 1,4-conjugate addition to the enantiopure cyclopentenonecarboxylate **11**.[1] This step was anticipated to proceed with the very dominant formation of **9** as a result of kinetically favored approach from that direction *syn* to the adjacent methyl substituent (Scheme 2). As matters worked out, the doubly activated nature of the Michael acceptor **11** facilitated capture of the organocopper species derived from **10**.[4] The conversion of **9** to **8**, or a variant of this system, was designed to allow assembly of a highly functionalized cyclopentene, whose cyclization under appropriate conditions would allow the generation of **7**. γ-Alkylation of this cyclohexenone with 4-iodo-1-butene[5] was to ensue, this step setting the stage for more advanced functional group manipulation within **6a**.

Aldehyde **12**, prepared in two steps from commercially available 1,4-butanediol, was methylenated in Mannich fashion[6] and reduced with sodium borohydride to furnish the allylic alcohol **13** (Scheme 3). Formation of iodide **14** was most efficiently accomplished by treatment with lithium chloride and methanesulfonyl chloride in DMF containing 2,6-lutidine, followed by the addition of sodium iodide.[7] The targeted oxazolidinone was generated through reaction of **14** with the sodium enolate of **15** with a de in excess of 95%.[8] Removal of the chiral auxiliary was smoothly achieved with $NaBH_4$. The carbinol **16** so formed was chemoselectively reduced in a two-step process involving initial production of the iodide followed by the action of tri-*n*-butyltin hydride.[9] Finally, the benzoate group was saponified and the resultant chiral alcohol was transformed without event into **10** by a closely related halogenation protocol.

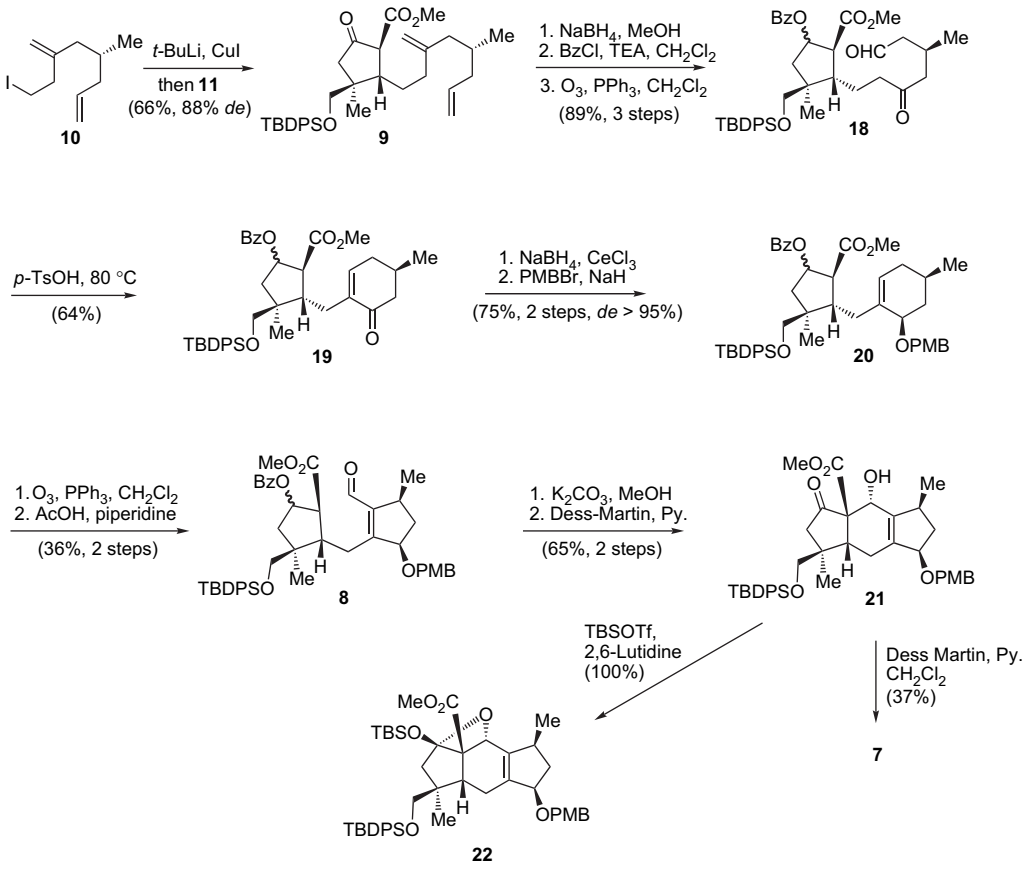
The coupling of iodide **10** to cyclopentenonecarboxylate **11** was most efficiently achieved using *tert*-butyllithium and CuI to form the cuprate. Under these conditions, **9** was isolated as a 16:1 mixture of diastereomers. With the benefit of COSY and NOESY experiments, the major isomer could be readily identified as the expected **9** (Scheme 4). Selective borohydride reduction of the ketone carbonyl in this intermediate gave rise to a 2:1 diastereomeric mixture of alcohols, which were protected as their benzoates. Subsequent reductive ozonolysis furnished the keto aldehyde **18**, which was directly cyclized to cyclohexenone **19** under acidic conditions. Recourse was next made to a Luche reduction



Scheme 2.



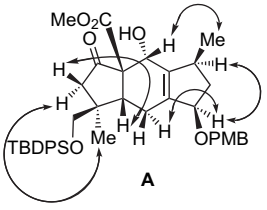
Scheme 3.



Scheme 4.

(de>95%) and subsequent formation of the *p*-methoxybenzyl ether. Ozonolytic of the trisubstituted double bond and ensuing cyclization of the resulting keto aldehyde with piperidine in acetic acid delivered **8** in 36% yield over the two steps.

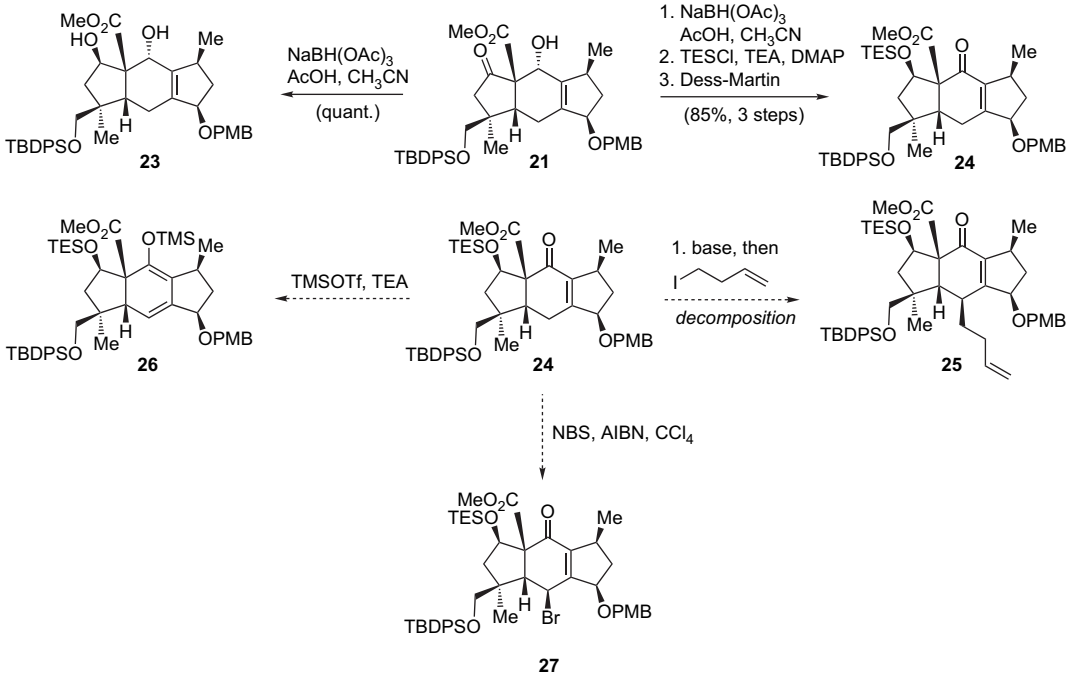
With aldehyde **8** in hand, the time had arrived for removal of the benzoate protecting group and regeneration of the β-keto ester functionality. Pleasingly, use of the Dess–Martin periodinane and pyridine in CH_2Cl_2 proceeded with in situ cyclization to generate the tricyclic aldol **21** as a 10:1 mixture of diastereomers at the allylic alcohol center. The first-stage oxidation is a very quick process (complete in less than 5 min) and cyclization ensues immediately. In contrast, the second-stage oxidation involving **21** is a rather slow process, which required 16 h to reach completion. The stereochemical assignments to **21** are soundly based on ^{1}H NMR, ^{13}C NMR, HMQC, and NOESY experiments (see **A**).



Transient protection of the secondary hydroxyl group in **21** came to be regarded as desirable. When initial attempts to accomplish this transformation with *tert*-butyldimethylsilyl or triethylsilyl chlorides were met with failure, presumably as a result of steric congestion, enhanced reactivity was sought in the form of *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine. These conditions resulted in formation of acetal **22** (100% yield).

Our arrival at the tricyclic intermediates **7** and **21** was met with the breakdown of many potentially useful transformations. For example, attempts to reduce the ester moiety in **21** with $LiAlH_4$ or DIBAL-H led to rather complex product mixtures. Similarly, while **21** could be chemoselectively reduced with sodium triacetoxyborohydride by way of intramolecular hydride transfer[10] with introduction of a β-hydroxyl subunit as in **23** (Scheme 5), controlled conversion to a monoxanthate was not possible as a prelude to tin hydride reduction.[11] Direct reduction of the ketone carbonyl in **21** via the formation of the tosylhydrazone[12] promoted wholesale degradation.

On a more positive note, treatment of **23** with triethylsilyl chloride served as a means for achieving efficient monoprotection. As a result, arrival at **24** proved not to be a challenge. Various options for the exploration of routes to the γ-alkylated product **25** could now begin. The most direct route involving generation of the extended anion of enone **24** and reaction with 4-iodo-1-butene was disadvantaged from the start due to a sensitivity of this intermediate to strong base. Upon admixture with a variety of bases, decomposition was seen to set in quickly in all cases. Experiments designed to generate the conjugated silyl enol ether **26**[13] and to



Scheme 5.

brominate the γ-position as in **27**[5a,14] were likewise met with failure. These and related problems prompted consideration of means for introduction of the butenyl group earlier in the synthesis.

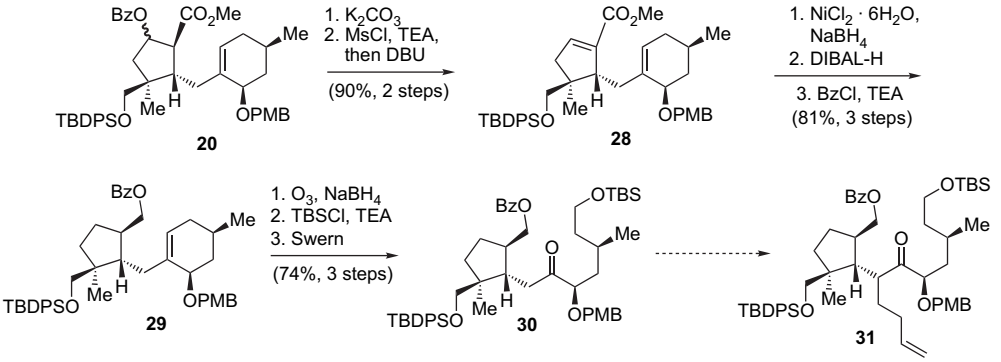
3. Consideration of earlier incorporation of the alkenyl chain

Ketone **30** was successfully prepared from **20** via the sequence outlined in Scheme 6.[15] The benzoate group was excised with potassium carbonate, and the secondary hydroxyl so uncovered was transformed into the mesylate. β-Elimination now became possible by treatment with DBU, and provided **28** in 90% overall yield. Next to be explored was selective reduction of the double bond conjugated with the carbomethoxy substituent. The utilization of $NaBH_4$ and $NiCl_2$ in tandem[16] proved quite amenable to this transformation. There followed the direct reduction to the primary carbinol with DIBAL-H and formation of the benzoate to furnish **29**. Continued success was realized with reductive ozonolysis of the remaining double bond in **29**. The diol so formed proved entirely accommodative of chemoselective O-silylation at the primary site with TBSCl. Finally, the targeted **30** was secured by the application of Swern oxidation conditions.

While the conversion of **20** to **30** proceeded quite satisfactorily, **30** resisted alkylation via its enolate at every turn. These attempts at functionalization included treatment with bases such as NaHMDS, KHMDS, LDA, NaH, and KH, as well as recourse to electrophiles exemplified by 4-bromo-1-butene, 4-iodo-1-butene, allyl bromide, methyl iodide, and gaseous formaldehyde. In the light of these developments, the decision was made to advance on these intermediates in an alternate fashion.

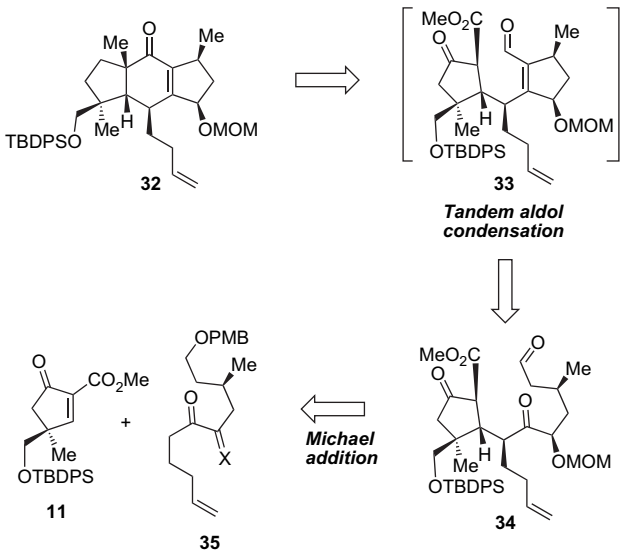
4. The quest for more direct assembly

The prominent complications witnessed so far for achieving proper alkylation of relevant advanced intermediates



Scheme 6.

emphasize the need for a strategic disconnection that makes provision for the earlier introduction of a suitable side chain. To this end, the involvement of **35** as a central building block was considered attractive (Scheme 7). The implementation of this plan called for site-specific deprotonation of **35** in advance of its Michael addition to **11**. The appeal offered by the framework where X was to be an appropriately configured protected carbinol center defined our original thrust in this direction. Further along the retrosynthetic pathway, **34** was to be cyclized to **33** in a manner paralleling the earlier conversion of **19** to **20**. The execution of a second-stage aldol ring closure followed by minor functional group adjustments was to lead to the tricyclic framework represented by **32**.

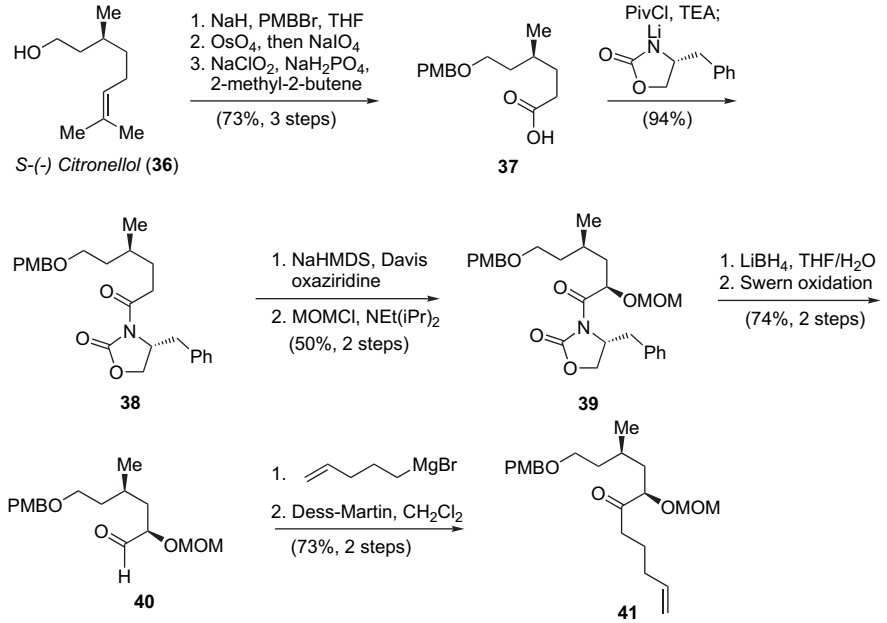


Scheme 7.

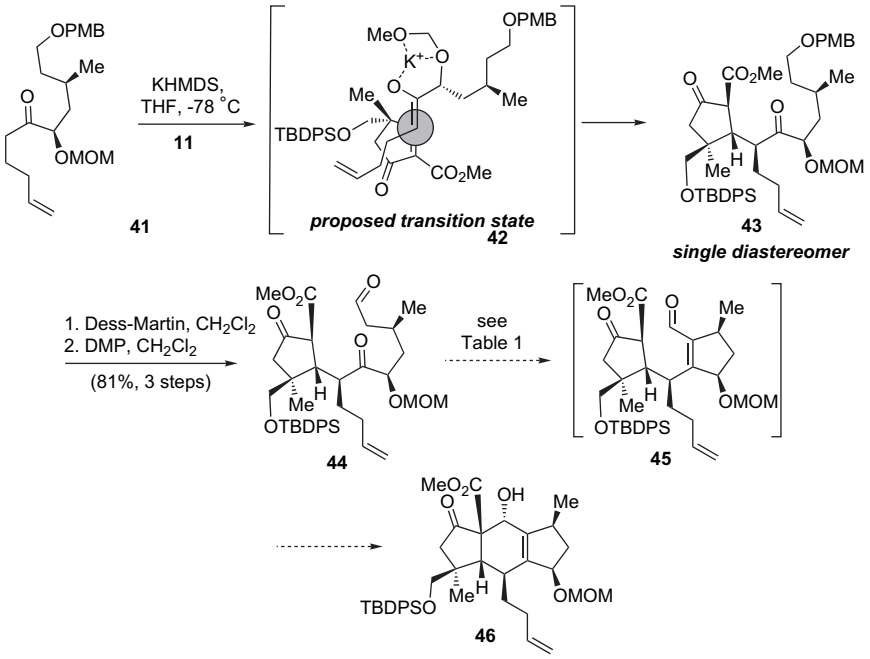
The conversion of *S*-citronellol (**36**) to carboxylic acid **37**, shown in Scheme 8, was conveniently accomplished in a three-step sequence consisting of PMB protection, double bond cleavage via the 1,2-diol, and oxidation with sodium chlorite.[17] The coupling of **37** to the Evans auxiliary (*R*)-4-benzyl-2-oxazolidinone[18] was mediated via the mixed anhydride generated with pivaloyl chloride. The availability of **38** allowed for the implementation of an enantioselective α-hydroxylation step involving the Davis oxaziridine.[19] Although a diastereomeric excess of 5:1 was realized, the enantiomeric purity could be readily enhanced to the 100% level by chromatographic separation of the pair of derived MOM ethers on silica gel. Since attempts to transform **39** into its Weinreb amide resulted in destruction of the material, an alternative pathway involving reduction to the alcohol and Swern oxidation provided aldehyde **40** in 74% overall yield. The route to **41** was then completed by 1,2-addition of 4-pentenylmagnesium bromide and exposure of the resulting carbinol to the Dess–Martin periodinane reagent.[20]

The deprotonation of **41** with KHMDS at −78 °C proceeded with high regioselectivity to generate the enolate anion depicted in **42** (Scheme 9). The intramolecular chelation involving the MOM substituent specifically defined in this transition state serves to enhance steric biases and allows for the specific formation of **43** as the only observed diastereomer. Chemoselective deprotection of the OPMB group was easily accomplished with DDQ in conventional fashion, thereby making possible ensuing periodinane oxidation to the highly functionalized diketo aldehyde **44** in 80% isolated yield.

When conditions previously developed by Hiranuma and Hudlicky[21] for intermolecular aldol condensations of the projected **44**→**45** type were examined (see Table 1, experiments 1 and 5), enamine formation was observed as in the other cases (^{1}H NMR analysis). However, this intermediate underwent no further chemical reaction and resisted cyclization on prolonged heating. Treatment of **44** in the manner devised in entries 2 and 3 of Table 1 resulted in clean amidation of the carbomethoxy group to give **47**, with this conversion



Scheme 8.



Scheme 9.

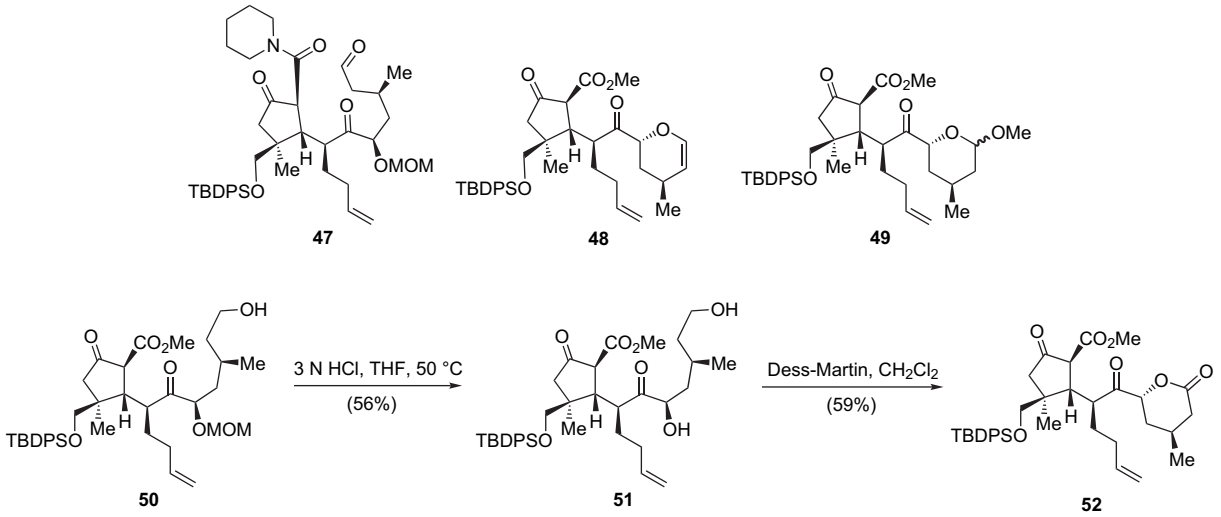
Table 1. Representative conditions applied to **44** for attempted cyclization

Expt.	Reagent	Solvent	Result
1	Piperidine, HOAc	Ether, reflux	Clean enamine formation
2	Piperidine, HOAc	Benzene, reflux	Slow conversion to **47**
3	Piperidine, HOAc	Toluene, reflux	Conversion to **47**
4	Martin sulfurane	CH_2Cl_2, rt	No reaction
5	Pyrrolidine, CSA	Ether, reflux	Clean enamine formation
6	CSA (Dean–Stark)	Benzene, reflux	Formation of **48** and **49**
7	$Et_2NH{\cdot}HCl$	$ClCH_2CH_2Cl$, 70 °C	MOM cleavage and lactol formation **48**

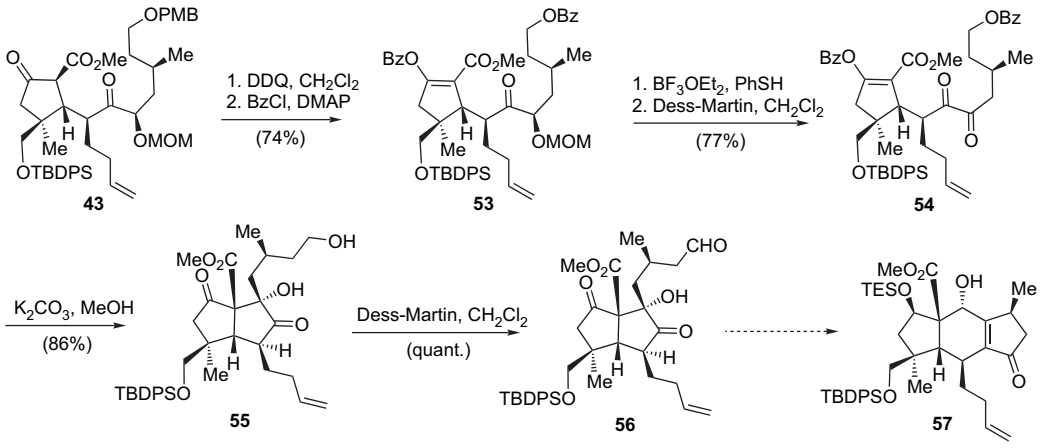
occurring faster in refluxing toluene solution as expected. Other notable transformations included MOM deprotection and subsequent cyclization with lactol formation when conditions such as those in experiment 7 were utilized. More advanced dehydrative elimination to generate the pyran **48** and lactol ether **49** was noted when **44** was heated with CSA in benzene under a Dean–Stark trap. A parallel direction was followed when **50**, the primary carbinol derived from **43** (Scheme 9), was further deprotected as in **51** and subjected to periodinane oxidation. When processed in this manner, lactone **52** was formed as the predominant product (Scheme 10).

5. Determining the suitability of aldol cyclizations for construction of the tricyclic core

We next investigated the possibility of forming a major portion of the mangicol A framework through an aldol ring-forming reaction. To enlist the proper regioselectivity, the strategy was designed to involve an α-diketone such as that resident in **54**. Although several reaction parameters

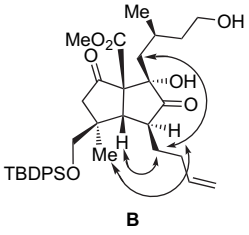


Scheme 10.



Scheme 11.

are thereby introduced, the added complexity was expected to shed light on which mode of cyclization would be kinetically favored. Another advantage would stem from the reversibility of aldol condensations, which could serve to clarify available thermodynamic options as well. Thus, **43** was transformed into enol benzoate **53**, thereby making possible removal of the MOM protection group[22] and mild oxidation to gain access to **54** (Scheme 11). The benzoate groups were then hydrolyzed with K_2CO_3 in methanol, a process during which spontaneous passage to diquinane **55** materialized. Although this eventuality was not the desired one, two positive consequences of this reaction pathway were made apparent. First, our provisional assignments to the configuration of several stereocenters could now be fully corroborated by NOE correlations (see **B**).

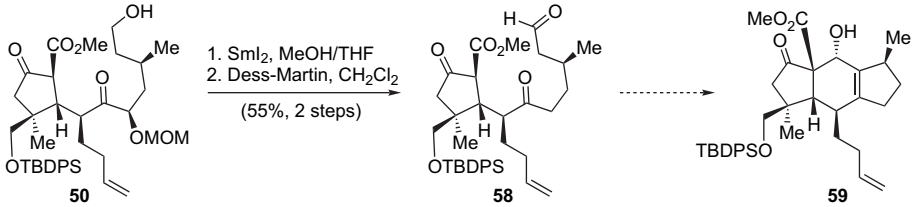


Secondly, the availability of **55** allowed for one-step conversion to aldehyde **56**. However, all attempts to bring about retroaldolization with **56** and alternative generation of **57** were to no avail, nor was any reaction observed when **58** was comparably exposed to a range of basic conditions. In fact, **56** and **58** are quite stable entities and can be stored on the shelf for prolonged periods of time.

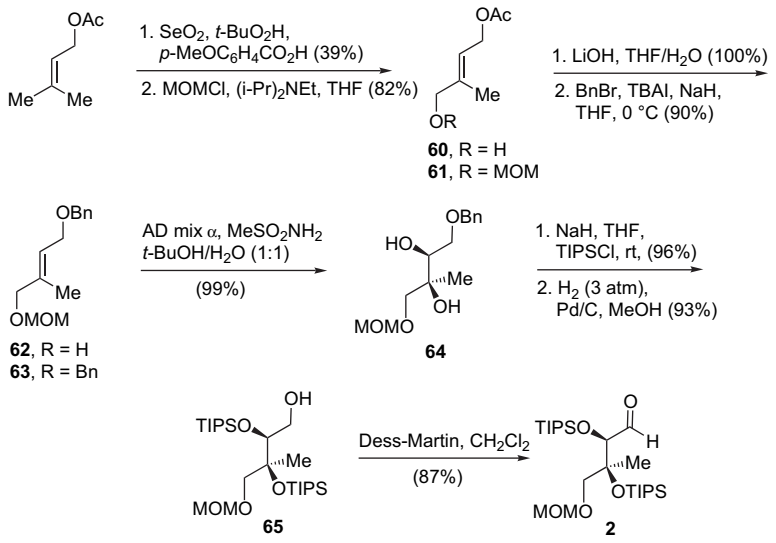
A final approach was envisioned to involve samarium diiodide reduction of carbinol **50** and subsequent Dess–Martin oxidation to obtain keto aldehyde **58**. We attempted the transformation of **58** to **59** by applying the same conditions as from **44** to **45**, with resultant in destruction of **58** (Scheme 12).

6. Synthesis of the side chain

The launching point for arrival at **2** was the allylic alcohol **60** previously shown by Mechelke and Wiemer[23] to be available in two steps from prenyl alcohol (Scheme 13). MOM protection of the hydroxyl group in **60** was followed by deacetylation and O-benzylation to deliver **63**. With this functionality in place, it proved straightforward to effect Sharpless asymmetric dihydroxylation[24] with AD-mix-α to afford **64** in 99% yield. This critical step was followed by reaction with triisopropylsilyl chloride in the presence of NaH, thus making possible chemoselective debenzylation[25] and generation of the primary alcohol **65**. This very efficient two-step process made possible the ultimate production of the targeted **2** via the Dess–Martin protocol.[20]



Scheme 12.



Scheme 13.

7. Overview

In this paper, we have detailed the ability of cyclopentenonecarboxylate **11** to serve as a Michael acceptor under two sets of circumstances. In the first instances, the employment of the cuprate derived from **10** as co-reagent proved to be beneficial since subsequent conversion to the tricyclic aldol **21** and diketone **7** was efficiently realized. Our inability to bring about the proper alkylation of these advanced intermediates prompted examination of a second approach, which involved the conjugate addition of the enolate of **41** to **11**. While the subsequent elaboration of **44** proceeded uneventfully, the intrinsic inability to bring about the appropriate cyclization at this stage highlighted the impact of a butenyl side chain on impeding ring formation. While these strategies ultimately prove unsuccessful, they are expected to facilitate further investigation of the synthetic chemistry of the mangicols. The availability of aldehyde **2** constitutes a positive step in that direction.

8. Experimental

8.1. Alkylation of oxazolidinone 15 with iodide 14. Reduction to the hydroxy benzoate

Oxazolidinone **15** (13.41 g, 51.7 mmol) was dissolved in dry THF (85 mL) and cooled to −78 °C at which point sodium hexamethyldisilazide (52 mL, 1.51 M) was introduced. The reaction mixture was stirred for 1 h when iodide **14** (12.3 g, 34.2 mmol) was added via cannula as a solution in dry THF (65 mL). After 3 h, reaction was judged to be completed and water was added. After warming to rt, the product was extracted into CH_2Cl_2 (3×100 mL) and the combined organic layers were dried and freed of solvent to leave an orange residue that was dissolved in MeOH (350 mL) at 0 °C. $NaBH_4$ (9.85 g, 0.26 mmol) was added in portions over a period of 30 min. The reaction mixture was stirred overnight, quenched with water, and extracted with ethyl acetate (3×350 mL). The combined organic layers were dried and the solvent was evaporated to leave an oil that solidified. Flash chromatography of the residue on silica gel (gradient–hexane–ethyl acetate=5:1 to 3:1) afforded 7.4 g (79%) of **16**; IR (neat, cm^{-1}) 3434, 1721, 1641; ^1H NMR (250 MHz, $CDCl_3$) δ 8.05–7.97 (m, 2H), 7.63–7.29 (m, 3H), 5.92–5.72 (m, 1H), 5.13–4.87 (m, 2H), 4.45 (dt, J=1.6, 6.9 Hz, 2H), 5.58 (d, J=5.3 Hz, 2H), 2.51 (t, J=6.8 Hz, 2H), 2.23–2.00 (m, 4H), 1.92–1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 143.5, 136.3, 132.6, 129.9, 129.2 (2C), 128.0 (2C), 127.0, 126.6, 116.2, 113.0, 64.4, 63.0, 38.0, 37.6, 34.1, 34.4; HRMS ES m/z $(M+Na)^+$ calcd 297.1461, obsd 297.1460.

8.2. Coupling of 10 with 11

A 250 mL round-bottomed flask was charged with **10** (4.06 g, 15.4 mmol) and ether (30 mL), and the solution was cooled to −78 °C while *t*-BuLi (18.2 mL, 1.7 M in pentane) was introduced. The mixture was stirred in the cold for 5 min, then transferred to a suspension of CuI (1.46 g, 7.67 mmol) in dry ether (20 mL) being stirred at −20 °C. The mixture was stirred for another 5 min, cooled to −30 °C, and treated with **11** (3.25 g, 9.64 mmol) as a solution in dry ether (25 mL). The reaction mixture developed a blue color while it was being stirred for another 50 min. After quenching with saturated NH_4Cl solution (200 mL), the product was extracted into CH_2Cl_2 (3×300 mL), the combined organic layers were dried, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=40:1 to 20:1) to give 2.86 g (66%) of **9** as a pale yellowish oil; IR (neat, cm^{-1}) 1757, 1730, 1640; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.60 (m, 4H), 7.60–7.32 (m, 6H), 5.87–5.65 (m, 1H), 5.07–4.92 (m, 2H), 4.72 (s, 2H), 3.75 (s, 3H), 3.60 (d, J=10.2 Hz, 1H), 3.49 (dd, J=10.2, 1.0 Hz, 1H), 3.10–2.77 (m, 3H), 2.13–1.20 (series of m, 9H), 1.10 (s, 9H), 0.88–0.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 170.4, 147.6, 137.1, 135.5 (4C), 133.1 (2C), 129.8 (2C), 127.7 (4C), 115.8, 110.7, 99.8, 67.3, 60.2, 52.4, 50.0, 43.9, 43.7, 42.7, 40.9, 34.4, 30.7, 28.1, 26.8 (3C), 19.3, 17.7; HRMS ES m/z $(M+Na)^+$ calcd 583.3214, obsd 583.3229; $[\alpha]_D^{20}$ 27.0 (c 1.07, C_6H_6).

8.3. Cyclohexenone 19

A solution of **9** (5.80 g, 10.3 mmol) in methanol (400 mL) was cooled to 0 °C, treated with $NaBH_4$ (783 mg, 20.6 mmol) over a period of 5 min, stirred for another 10 min, quenched with water (250 mL), and extracted with CH_2Cl_2 (3×400 mL). The combined organic layers were dried and evaporated to give 6.0 g (100%) of the β-hydroxy ester as a pale yellow foam which was not further purified; IR (neat, cm^{-1}) 3455, 1734, 1641; ^1H NMR (250 MHz, $CDCl_3$, mixture of diastereomers) δ 7.75–7.63 (m, 4H), 7.48–7.28 (m, 6H), 5.84–5.63 (m, 1H), 5.05–4.93 (m, 2H), 4.68 (d, J=5.0 Hz, 2H), 4.42–4.25 (m, 1H), 3.77–3.68 (m, 3H), 3.41 (s, 1H), 3.35 (d, J=1.1 Hz, 1H), 2.67–2.50 (m, 2H), 2.40–1.12 (series of m, 9H), 1.00–0.72 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 175.7 and 173.9, 148.2 and 148.2, 137.3, 135.8 (4C), 133.5 (2C) and 132.9 (2C), 129.8 (2C), 127.6 (4C), 115.8, 110.4 and 110.3, 100.0, 75.9, 72.5, 71.3, 70.5, 59.4, 56.3, 53.8, 51.7, 47.2, 45.4, 45.2, 43.7, 43.5, 41.0, 34.6 and 34.3, 30.7, 29.9, 29.4, 28.7 and 28.6, 26.9 and 26.8, 20.5, 20.2, 19.3; HRMS ES m/z $(M+Na)^+$ calcd 585.3371, obsd 585.3351.

The alcohol above (117 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (5 mL), cooled to 0 °C, and treated sequentially with triethylamine (0.15 mL, 1.04 mmol), benzoyl chloride (75 μL, 0.62 mmol), and DMAP (25 mg, 0.21 mmol). The reaction mixture was stirred for 9 h, quenched with water (20 mL), and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried and evaporated to dryness. The residue was purified by chromatography on silica gel (gradient–hexane to hexane–ethyl acetate=10:1) to give 124 mg (89%) of the benzoate as a colorless oil; IR (neat, cm^{-1}) 1740, 1722; ^1H NMR (250 MHz, $CDCl_3$, mixture of diastereomers) δ 8.08–7.92 (m, 2H), 7.70–7.23 (series of m, 13H), 5.82–5.62 (m, 1.6H) and 5.53–5.42 (m, 0.4H), 5.05–4.97 (m, 1H), 4.95 (s, 1H), 4.73–4.64 (m, 2H), 3.74 (s, 1.1H) and 3.57 (s, 1.6H), 3.56–3.43 (m, 2H), 2.98 (dd, J=10.3, 8.0 Hz, 0.6H), 2.84 (dd, J=10.7, 5.3 Hz, 0.4H), 2.50–2.61 (m, 0.7H), 2.55 (dd, J=14.2, 8.0 Hz, 0.4H), 2.44–2.30 (m, 0.5H), 2.22 (dd, J=13.5, 4.9 Hz, 0.7H), 2.13–1.20 (series of m, 9H), 1.10 (s, 3H), 1.06 (s, 9H), 0.83 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 175.2 and 172.2, 165.7 and 165.5, 148.0 and 147.9, 135.6 (4C), 133.3 (2C), 130.1 and 129.6 (2C), 127.6 and 127.5 (4C), 115.7 and 115.7, 110.5 and 110.3, 74.3, 70.9 and 69.4, 57.4, 53.7, 53.3, 51.8 and 51.5, 46.8, 46.4, 45.1, 44.8, 43.6, 43.0, 42.6, 41.0, 34.4 and 34.1, 30.6, 28.6 and 28.4, 26.8 (3C), 19.3 and 19.0, 19.2; HRMS ES m/z $(M+Na)^+$ calcd 689.3633, obsd 689.3616.

The benzoyl ester (7.2 g, 10.8 mmol) from above was dissolved in a 1:1 CH_2Cl_2–MeOH mixture (500 mL), cooled to −78 °C, and ozonolyzed until a blue color persisted. After purging with oxygen, triphenylphosphine (4.25 g, 16.2 mmol) was added and the solution was warmed to rt. The solvent was evaporated and the white solid was dissolved in dry benzene (150 mL). The benzene was evaporated again and the remaining solid was redissolved in dry benzene (600 mL). *p*-Toluenesulfonic acid (1.08 g, 5.6 mmol) was introduced and the mixture was heated at 75 °C overnight, cooled to rt, and freed of solvent. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=10:1 to 5:1) to give 4.48 g (64%) of pure **19**; IR (neat, cm^{-1}) 1721, 1677; ^1H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 8.06–8.00 (m, 0.7H), 7.97–7.90 (m, 1.3H), 7.74–7.62 (m, 5H), 7.62–7.28 (m, 8H), 6.69–6.60 (m, 1H), 5.66 (dd, J=14.4, 6.4 Hz, 0.8H), 5.47–5.37 (m, 0.2H), 3.66 (s, 1H), 3.56 (dd, J=13.7, 9.9 Hz, 1H), 3.49 (s, 3H), 3.03 (dd, J=10.9, 8.1 Hz, 0.7H), 2.83 (dd, J=10.7, 5.3 Hz, 0.3H), 2.75 (dt, J=10.8, 4.3 Hz, 0.7H), 2.60–1.77 (series of m, 9H), 1.73 (dd, J=14.2, 3.2 Hz, 0.3H), 1.10 (s, 2.1H) and 1.09 (s, 0.7H), 1.06 (s, 9H), 1.00 (d, J=6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 198.8 and 198.5, 174.5 and 171.7, 165.6 and 165.3, 145.3 and 144.8, 137.9 and 137.2, 135.5 (4C), 133.4 (2C), 132.7, 129.8, 129.5 (2C), 129.4 (2C), 129.1 (2C), 127.5 (2C), 77.4, 70.3 and 69.9, 56.7, 53.2, 51.7 and 51.4, 46.3 and 46.2, 45.5, 45.4 and 45.3, 44.3, 43.3 and 42.9, 34.3 and 34.2, 30.3 and 30.2, 29.7 and 29.4, 26.7, 21.2, 19.3, 19.2; HRMS ES m/z $(M+Na)^+$ calcd 675.3112, obsd 675.3129.

8.4. Unsaturated aldehyde 8

A solution of **20** (1.55 g, 2.00 mmol) in 1:1 MeOH–CH_2Cl_2 was cooled to −78 °C, ozonolyzed until a blue color persisted, and purged with oxygen for 15 min. Triphenylphosphine (784 mg, 3.00 mmol) was added, the reaction mixture was warmed to rt, the solvent was evaporated, and the residue was dissolved in dry ether (125 mL) and repeatedly evaporated to dryness. At this point, dry ether (100 mL) and piperidine (100 μL, 1.00 mmol) were added. After 5 min, AcOH (57 μL, 1.00) was introduced, and the mixture was heated to reflux for 4 days. Flash column chromatography of the residue after solvent evaporation (hexane–ethyl acetate=5:1) furnished 0.53 g (36%) of **8**; ^1H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 10.06 (s, 0.5H) and 10.05 (s, 0.5H), 8.09–7.88 (m, 2H), 7.72–7.20 (m, 13H), 7.12–7.00 (m, 0.4H), 6.85 (d, J=8.6 Hz, 1H), 6.75–6.66 (m, 0.4H), 5.72–5.60 (m, 0.4H), 5.56–5.47 (m, 0.4H), 4.57–4.27 (m, 3H), 3.82 (s, 0.4H), 3.78 (s, 2.6H), 3.76–3.70 (m, 0.4H), 3.60 (s, 1H), 3.49 (s, 1H), 3.46–3.30 (m, 1H), 3.28 (d, J=10.0 Hz, 0.4H), 3.10–1.90 (series of m, 10.6H), 1.70 (dd, J=14.5, 2.49 Hz, 0.4H), 1.40–1.20 (m, 1.3H), 1.17 (s, 1.5H), 1.11 (s, 4.5H), 1.08 (s, 1.5H), 1.05 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 189.0 and 188.9, 174.1 and 171.2, 165.9 and 165.6, 160.2 and 159.3, 143.3 and 143.0, 135.7 (4C), 133.1, 130.3, 130.2, 130.1, 129.9, 129.8, 129.7 (2C), 129.6 (2C), 129.5, 129.3, 129.2, 128.4, 127.8, 113.8, 99.7, 83.8, 77.2 and 73.6, 71.7 and 71.5, 70.1 and 69.7, 57.1, 55.2, 53.3, 52.0 and 51.8, 47.0 and 45.1, 45.9 and 44.2, 43.4 and 43.2, 37.1 and 37.0, 36.5 and 36.4, 26.9 (3C), 25.8 and 25.7, 20.5 and 20.4, 19.4 and 19.3, 19.1 and 18.7; HRMS ES m/z $(M+Na)^+$ calcd 811.3637, obsd 811.3635.

8.5. α-Oxygenation of 38 and MOM protection

To a solution of **38** (48.9 mg, 0.12 mmol) in dry THF (1.5 mL) was added sodium hexamethyldisilazide (141 μL, 0.141 mmol, 1 M in THF) at −78 °C. The mixture was stirred for 30 min, treated with the Davis reagent (39.9 mg, 0.15 mmol) dissolved in dry THF (1 mL) in a dropwise manner and quenched after 10 min with a solution of camphorsulfonic acid (137 mg, 0.59 mmol) in THF (0.9 mL). The

cooling bath was removed, the white slurry was stirred for 20 min, water (20 mL) and ether were added, and the product was extracted into CH_2Cl_2 (4×10 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=7:1 to 4:1) to give a colorless oil (37.7 mg, 74%) as a mixture of α-hydroxylated diastereomers (de 76%); IR (neat, cm^{-1}) 1783, 1697, 1247; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.13 (m, 7H), 6.87 (dt, J=8.6, 2.8 Hz, 2H), 5.07 (br d, J=7.2 Hz, 1H), 4.78–4.70 (m, 1H), 4.43 (dd, J=15.4, 11.5, 2H), 4.27–4.19 (m, 2H), 3.80 (s, 3H), 3.44–3.13 (m, 3H), 3.19 (dd, J=13.5, 3.2 Hz, 1H), 2.83 (dd, J=13.4, 9.3 Hz, 1H), 2.03–1.46 (series of m, 5H), 0.98 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.1, 153.2, 134.9, 130.8, 129.5 (2C), 129.3 (2C), 129.1 (2C), 127.5, 113.7 (2C), 72.5, 69.4, 68.3, 66.9, 55.5, 55.3, 41.3, 37.5, 35.3, 27.1, 20.6; HRMS ES m/z $(M+Na)^+$ calcd 464.2044, obsd 464.2062; $[\alpha]_D^{20}$ −29.2 (c 1.89, $CHCl_3$).

The above product (246 mg, 0.56 mmol) was dissolved in dry CH_2Cl_2 (6 mL) and diisopropylethylamine (573 μL, 3.35 mmol) was added. The reaction mixture was cooled to 0 °C and MOMCl (252 μL, 3.35 mmol) was introduced and stirring was maintained overnight. Half-saturated NH_4Cl solution (5 mL) was introduced, the aqueous layer was extracted with CH_2Cl_2 (4×4 mL), and the combined organic layers were filtered and evaporated to dryness. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=7:1 to 4:1) to provide 180 mg (67%) of **39** as a single diastereomer; IR (neat, cm^{-1}) 1780, 1708, 1642; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.13 (m, 7H), 6.86 (d, J=8.6 Hz, 2H), 5.36 (dd, J=7.4, 5.5 Hz, 1H), 4.77 (d, J=6.9 Hz, 1H), 4.57–4.20 (m, 4H), 4.42 (dd, J=17.4, 11.5 Hz, 2H), 4.16 (d, J=5.2 Hz, 2H), 3.79 (s, 3H), 3.54–3.44 (m, 2H), 3.38 (s, 3H), 3.32 (dd, J=13.1, 3.0 Hz, 1H), 2.79 (dd, J=13.4, 9.5 Hz, 1H), 2.00–1.78 (m, 2H), 1.72–1.57 (m, 3H), 1.46–1.30 (m, 1H), 0.96 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.0, 153.0, 135.2, 130.9, 129.5 (2C), 129.2 (2C), 129.0 (2C), 127.4, 113.7 (2C), 97.5, 74.5, 72.5, 68.0, 66.4, 56.3, 55.3 (2C), 40.4, 37.5, 35.3, 26.8, 20.5; HRMS ES m/z $(M+Na)^+$ calcd 508.2306, obsd 508.2320; $[\alpha]_D^{20}$ −27.2 (c 1.24, $CHCl_3$).

8.6. Ketone 41

5-Bromopentene (2.19 mL, 19.7 mmol) was added to a suspension of activated Mg turnings (478 mg, 19.7 mmol) in dry ether (27 mL) and a crystal of I_2. After 1 h, a solution of **40** in ether cooled to −78 °C was introduced via cannula. The reaction mixture was stirred for 30 min at −78 °C and for 20 min at 0 °C prior to quenching with saturated NH_4Cl solution and extraction with ether. The residue was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=7:1 to 5:1) to give the alcohol (1.37 g, 85%). The alcohol (1.37 g) was immediately oxidized to **41**. Dissolution in dry CH_2Cl_2 (42 mL) and pyridine (3.2 mL, 31.0 mmol) preceded addition of the Dess–Martin periodinane (3.43 mg, 9.0 mmol). The reaction mixture was stirred overnight and quenched with a 1:1 $Na_2S_2O_3$–$NaHCO_3$ solution (40 mL). The biphasic mixture was stirred for 3 h, and extracted with ether (3×30 mL). The combined organic layers were dried and evaporated to dryness under high vacuum to leave a residue that was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=25:1 to 10:1) to give 1.17 g (86%) of **41**; IR (neat, cm^{-1}) 1716, 1613, 1514; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J=9.0 Hz, 2H), 6.87 (d, J=9.0 Hz, 2H), 5.84–5.67 (m, 1H), 5.06–4.94 (m, 2H), 4.59 (dd, J=10.1, 6.9 Hz, 2H), 4.41 (dd, J=11.6, 10.1 Hz, 2H), 4.07 (dd, J=8.1, 5.4 Hz, 1H), 3.80 (s, 3H), 3.57–3.48 (m, 2H), 3.33 (s, 3H), 2.47 (t, J=7.2 Hz, 2H), 2.04 (q, J=4.4 Hz, 2H), 1.38–1.33 (m, 5H), 0.93 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 130.6, 129.2 (2C), 115.2, 113.7 (2C), 96.5, 81.0, 72.6, 67.9, 56.1, 55.3, 39.4, 37.2, 35.7, 33.1, 26.7, 22.3, 20.3; HRMS ES m/z $(M+Na)^+$ calcd 401.2298, obsd 401.2301; $[\alpha]_D^{20}$ −24.2 (c 1.54, $CHCl_3$).

8.7. Coupling of 41 to 11. Deprotection of 43

Ketone **41** (538 mg, 1.42 mmol) was dissolved in dry THF (6.7 mL) and potassium hexamethyldisilazide (2.84 mL, 1.42 mmol, 0.5 M in toluene) was added at −78 °C within 20 s. The mixture turned red after the addition of the first drops and finally changed to an orange solution after a few minutes. Stirring was maintained at −78 °C for 1 h. A solution of **11** (500 mg, 1.18 mmol) in dry THF (3.6 mL) precooled at −78 °C was transferred in and stirring was maintained for 5 min prior to quenching with saturated NH_4Cl solution (20 mL). After extraction with ether (3×20 mL), the combined organic layers were dried and evaporated to leave an oil that was purified by rapid filtration chromatography through silica gel to afford 716 mg of **43**.

Coupling product **43** (1.28 g, 1.60 mmol) was dissolved in 10:1 CH_2Cl_2–H_2O (47 mL) and DDQ (544 mg, 2.40 mmol) was introduced. The reaction mixture turned green-black within seconds and after some minutes became intense orange in color. The product was extracted into CH_2Cl_2 (3×20 mL), and the combined organic layers were dried and evaporated to leave a residue that was purified by column chromatography on silica gel (gradient–hexane–ethyl acetate=8:1 to 3:1) to give a total of 826 mg (76%) of pure carbinol as a colorless oil, along with 119 mg of a mixed fraction which was further purified to give 878 mg (81%) of **50**; IR (neat, cm^{-1}) 3512, 1751, 1726; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.18 (m, 4H), 7.50–7.34 (m, 6H), 5.73–5.55 (m, 1H), 5.00–4.90 (m, 2H), 4.55 (dd, J=12.3, 6.8 Hz, 2H), 4.00 (t, J=4.0 Hz, 1H), 3.80–3.55 (m, 5H), 3.73 (s, 3H), 3.49–3.30 (m, 2H), 3.30 (s, 3H), 2.94 (dd, J=8.1, 5.7 Hz, 1H), 2.53 (dd, J=17.6, 1.3 Hz, 1H), 2.30 (d, J=17.6 Hz, 1H), 2.10–1.18 (m, 9H), 1.14 (s, 3H), 1.03 (s, 9H), 0.89 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 208.8, 170.5, 137.2, 135.8 (4C), 132.6, 132.4, 130.0 (4C), 127.8 (2C), 115.6, 96.3, 80.3, 68.3, 60.3, 60.2, 56.2, 52.6, 51.7, 48.0, 45.9, 43.0, 38.8, 37.9, 30.3, 29.7, 29.2, 26.7 (3C), 26.1, 24.2, 20.3, 19.1; HRMS ES m/z $(M+Na)^+$ calcd 703.3642, obsd 703.3637; $[\alpha]_D^{20}$ −18.4 (c 4.12, $CHCl_3$).

8.8. Diquinane 55

Diketone **54** (79.3 mg, 0.094 mmol) was dissolved in MeOH (4.8 mL), potassium carbonate (172.9 mg, 1.25 mmol) was added, and the suspension was stirred at rt for 4 h until the reaction mixture was quenched with saturated NH_4Cl

solution (5 mL), and extracted with ether (4×3 mL). The combined organic layers were dried and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=2:1 to 1:1) to yield **55** (48.1 mg, 80%); IR (neat, cm^{-1}) 3431, 1708, 1218; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (m, 4H), 7.48–7.34 (m, 6H), 5.73–5.62 (m, 1H), 5.0–4.90 (m, 2H), 3.78–3.58 (m, 3H), 3.64 (s, 3H), 3.38–3.30 (m, 2H), 2.50 (t, J=6.5 Hz, 1H), 2.40 (d, J=15.5 Hz, 1H), 2.34 (dd, J=12.5, 7.0 Hz, 1H), 2.10–1.95 (m, 2H), 1.84 (dt, J=6.5, 6.5 Hz, 1H), 1.72–1.61 (m, 1H), 1.62–1.48 (m, 2H), 1.40–1.30 (m, 1H), 1.08 (s, 9H), 1.06 (s, 3H), 0.87 (d, J=5.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 175.4, 167.3, 157.7, 147.8, 137.5, 135.7 (2C), 132.9 (2C), 129.8, 127.7 (2C), 115.4, 69.5, 60.5, 52.0, 51.3, 47.7, 42.4, 38.9, 38.2, 32.8, 30.7, 30.0, 29.7, 29.6, 26.9 (3C), 20.6, 20.1, 19.3; HRMS ES m/z $(M+Na)^+$ calcd 657.3224, obsd 657.3206; $[\alpha]_D^{20}$ −31.12 (c 1.12, $CHCl_3$).

8.9. Aldehyde 58

Alcohol **50** (249.9 mg, 0.368 mmol) was dissolved in a 2:1 THF–MeOH mixture (13 mL) and SmI_2 was added until the deep blue color persisted (5.4 mL, 0.54 M suspension in THF). Stirring was continued for another 15 min, and the reaction mixture was quenched with a 1:1 THF–H_2O mixture (10 mL) when the color disappeared. Then HCl (2 mL, 2 N solution) followed by water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (gradient–hexane–ethyl acetate=4:1 to 3:1) to afford 189.4 (83%) of pure product; IR (neat, cm^{-1}) 3513, 1757, 1728, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.54 (m, 4H), 7.52–7.33 (m, 6H), 5.65–5.48 (m, 1H), 4.99–4.86 (m, 2H), 3.78–3.64 (m, 1H), 3.70 (s, 3H), 3.59 (d, J=10.4 Hz, 1H), 3.45–3.37 (m, 1H), 3.37 (d, J=10.4 Hz, 1H), 2.83–2.70 (m, 2H), 2.47 (d, J=18.0 Hz, 1H), 2.33 (d, J=18.0 Hz, 1H), 2.40–2.30 (m, 1H), 1.90–1.15 (series of m, 9H), 1.13 (s, 3H), 1.06 (s, 9H), 0.88 (d, J=5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 208.7, 170.4, 137.3, 136.2, 135.7, 132.9, 132.2, 130.2, 127.9, 127.7, 115.5, 69.0, 60.8, 60.5, 52.6, 52.3, 52.1, 49.6, 43.2, 39.6, 30.9, 29.4, 28.8, 26.9, 24.8, 19.4, 17.9; HRMS ES m/z $(M+Na)^+$ calcd 643.3451, obsd 643.3599; $[\alpha]_D^{20}$ −40.09 (c 1.39, $CHCl_3$).

The above alcohol (170.9 mg, 0.275 mmol) was dissolved in dry CH_2Cl_2 (34 mL), Dess–Martin periodinane (209.1 mg, 0.550 mmol) was added, the mixture was stirred for 1.5 h, quenched by the addition of saturated 1:1 $Na_2S_2O_3$–$NaHCO_3$ solution (10 mL), and extracted with ether (3×25 mL). The combined organic layers were dried and evaporated to give a residue that was purified by flash chromatography on silica gel (hexane–ethyl acetate=4:1) to give pure **58** (164.6, 91%); IR (neat, cm^{-1}) 1757, 1726, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, J=2.0 Hz, 1H), 7.72–7.52 (m, 4H), 7.52–7.32 (m, 6H), 5.66–5.47 (m, 1H), 5.96–4.84 (m, 2H), 3.72–3.62 (m, 1H), 3.67 (s, 3H), 3.58 (d, J=10.5 Hz, 1H), 3.94–3.86 (m, 1H), 3.36 (d, J=10.5 Hz, 1H), 2.81–2.67 (m, 2H), 2.46 (d, J=18.0 Hz, 1H), 2.42–2.30 (m, 2H), 2.23 (dd, J=7.7, 5.4 Hz, 1H), 2.60–1.15 (series of m, 6H), 1.11 (s, 3H), 1.07 (s, 9H), 0.91 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 208.5, 202.2, 170.3, 137.2, 135.8 (4C), 132.4, 132.0, 130.2 (2C), 127.9 (4C), 115.6, 69.0, 60.8, 52.6, 52.2, 52.1, 50.9, 49.7, 42.7, 42.5, 31.0, 30.9, 29.7, 27.3, 27.0 (3H), 24.8, 19.6, 18.9; HRMS ES m/z $(M+Na)^+$ calcd 641.3274, obsd 641.3297; $[\alpha]_D^{20}$ −40.0 (c 1.03, $CHCl_3$).

8.10. Asymmetric dihydroxylation of 63

AD-mix-α [1.19 g containing 2.0 mg of $K_2OsO_4\cdot 2H_2O$, 6.5 mg of $(DHQ)_2$–PHAL, 0.35 g of K_2CO_3, and 0.83 g of $K_3Fe(CN)_6$] was added to 8.6 mL of a 1:1 H_2O–*tert*-butyl alcohol solvent system. The mixture was stirred vigorously at rt until dissolution was complete. Methanesufonamide (81 mg, 0.85 mmol) was introduced, the reaction mixture was cooled to 0 °C, and **63** (200 mg, 0.85 mmol) was added in one portion. After 20 h in the cold, the reaction mixture was quenched with solid Na_2SO_3 (1.30 g, 12.62 mmol), allowed to warm to rt for 1 h, and extracted with ethyl acetate (5×10 mL). The combined organic extracts were washed with 2 M KOH (5 mL), dried, and concentrated prior to flash chromatography on silica gel (hexane–ethyl acetate=2:3). There was isolated 230 mg (99%) of **64** as a colorless oil; IR (neat, cm^{-1}) 3460, 1454, 1110; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.63 (s, 2H), 4.57 (s, 2H), 3.83 (dt, J=6.3, 4.0 Hz, 1H), 3.73–3.61 (m, 2H), 3.59 (d, J=9.7 Hz, 1H), 3.49 (d, J=9.7 Hz, 2H), 3.36 (s, 3H), 3.03 (s, 1H), 2.96 (d, J=4.4 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.5 (2C), 127.8, 127.7 (2C), 99.7, 96.9, 73.6, 73.2, 73.0, 72.7, 71.1, 55.3, 21.0; HRMS ES m/z $(M+Na)^+$ calcd 293.1359, obsd 293.1356; $[\alpha]_D^{20}$ −10.1 (c 1.25, $CHCl_3$).

Acknowledgements

S.P. is indebted to the Austrian Science Fund (FWF) for the award of an Erwin Schrödinger postdoctoral fellowship (project number: J2402).

Supplementary data

Experimental details for all compounds except for **8**, **9**, **16**, **19**, **39**, **41**, **43**, **50**, **55**, **58**, and **56**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.066.

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