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# THE ASYMMETRIC BAYLIS-HILLMAN REACTION AS A TEMPLATE IN ORGANIC SYNTHESIS

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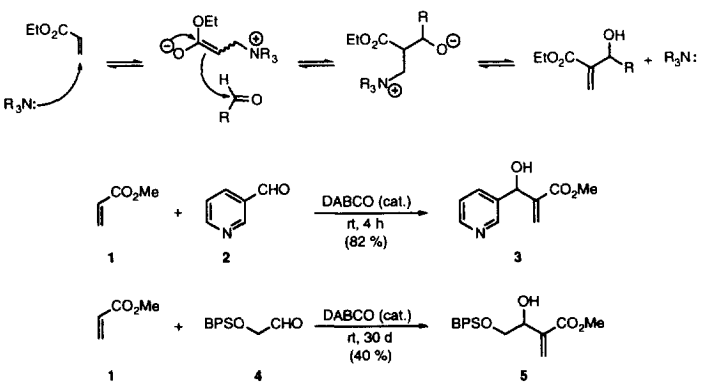
**Abstract:** The Baylis-Hillman reaction of camphor-based acrylates has been demonstrated to result in the formation of products with high optical purity. A model that explains these results and the use of these products in the formation of anti aldol adducts is discussed. © 1997 Elsevier Science Ltd.

One of the greatest challenges that organic chemists have tackled is the synthesis of organic compounds with complete control of stereochemistry. Considerable effort has been expended in the development of stereocontrolled reactions and the understanding of stereochemical communication. As the need for enantiomerically pure materials has come to the fore, methods for the use of readily available members of the chiral pool as starting materials, auxiliaries and catalysts have become an increasingly important research focus.[1] While a number of powerful transformations have been discovered in this pursuit, there is still a tremendous need for additional and alternative procedures that may improve upon or complement these techniques.

One method for the construction of carbon-carbon bonds that has attracted recent interest is the Baylis-Hillman reaction.[2] This reaction involves the tertiary amine-catalyzed addition of an acrylate to an aldehyde (Scheme I). Michael addition of the catalyst to the acrylate is followed by an aldol addition and subsequent

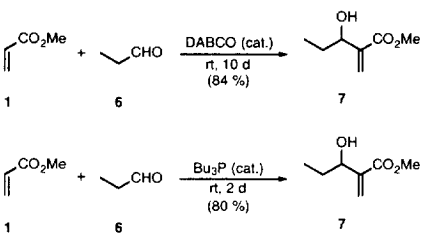
Scheme I



elimination, which regenerates the catalytic nucleophile. Since the result is the formation of a carbon-carbon bond to give an acrylate with an allylic stereocenter, it is ripe with possibilities as a synthetic tool, should an asymmetric variation be achieved.[3] It should be mentioned, however, that the Baylis-Hillman reaction has a considerable shortcoming in that it can be an excruciatingly slow transformation,[2] with reaction times of greater than one month not uncommon.[4] In order for the reaction to become a practical tool in organic synthesis, this issue must also be addressed.

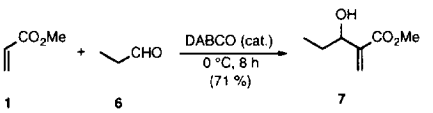
There have been several reports of attempts to accelerate the Baylis-Hillman reaction.[2] In addition to variations of catalysts and solvents, modifications such as the use of high pressure[5] and microwaves[6] have given some promising results but have not become the ideal solution. In our hands, we found that the use of trialkylphosphines as catalysts were a useful improvement.[7,8] While addition of methyl acrylate to propionaldehyde required 10 days to reach completion under standard Baylis-Hillman conditions with DABCO, the reaction was complete in just 2 days with tributylphosphine (Scheme II). In fact, we found that tributylphosphine was the best catalyst for the addition of methyl acrylate to a variety of aldehydes at room temperature.[9]

Scheme II




Although this improvement in the rate was a potentially useful discovery, we found that the yields typically obtained in the Baylis-Hillman reaction were lower when performed on a larger scale. It had previously been established that the Baylis-Hillman reaction was not very amenable to heating.[10] While gentle heating had been found to accelerate the process in isolated instances, it generally had a deleterious effect on the outcome, owing in large part to polymerization of the acrylate.[10] Concerned that localized heating may have been a problem on scale-up, we investigated the effects of initiating the reaction at low temperature. To our surprise, the reaction occurred much more quickly at 0 °C than at room temperature (Scheme III).[11] This acceleration was substantially more pronounced than that previously observed by the use of a trialkylphosphine catalyst, allowing us to return to the use of tertiary amines. However, the tributylphosphine catalysis should not be discounted, as it allows for the potential use of base sensitive aldehyde substrates in the Baylis-Hillman reaction.

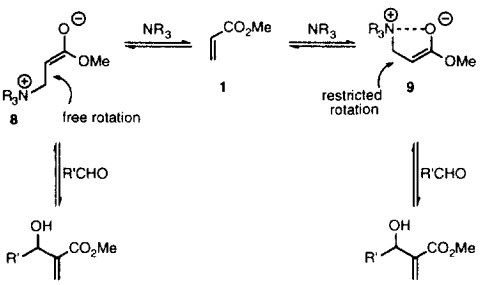
Scheme III




The temperature effect on the Baylis-Hillman reaction is somewhat counterintuitive in that the formation of product is apparently accelerated by either heating or cooling the reaction. The reasons for this are not yet completely understood, but one potential explanation is that the product is being formed via two different intermediates. The Michael addition of the catalyst into the acrylate can lead to two different enolates (**8** and **9**, Scheme IV). In the *E*-enolate (**9**), the ionic attraction between the anionic oxygen and the quaternary ammonium cation creates an isoxazoline-like intermediate. Conversely, the *Z*-enolate (**8**) cannot exhibit this ionic

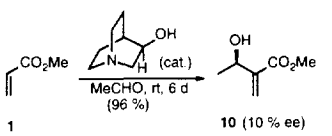
attraction. Both of these enolates should be formed under equilibrating conditions, and both likely react with aldehydes at different rates. This difference in rates would likely arise from the restricted rotation of the α,β-bond in **9** due to the ionic attraction of the charged atoms. It is possible that the apparent rate effects observed at different temperatures in the Baylis-Hillman reaction reflect the relative equilibria associated with these two enolates. A greater population of the more reactive enolate might exist at 0 °C, leading to a more rapid formation of the product. Work is currently underway to elucidate the nature of this unusual temperature effect.

Scheme IV



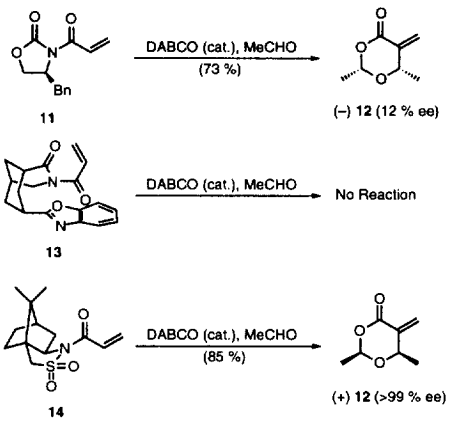

While the low-temperature acceleration was a useful improvement in the practicality of the Baylis-Hillman reaction, we still needed to address the issue of enantiocontrol. The fact that the reaction is catalyzed by tertiary amines offers the tantalizing prospect of using a chiral catalyst as a means of introducing stereochemistry, especially in light of the plethora of alkaloids available.[2] Unfortunately, these catalysts lead to virtually no asymmetric induction.[2] In fact, the best results we were able to observe were with optically enriched 3-quinuclidinol (Scheme V), but even this result was very discouraging.

Scheme V



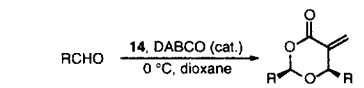

The use of chiral auxiliaries in the Baylis-Hillman reaction has also been explored.[2] While chiral acrylate esters have given relatively poor results under standard conditions,[11] little work had been reported on the use of chiral imides. We therefore examined the use of auxiliaries such as chiral oxazolidinones in this regard (Scheme VI).[12] We were surprised to find that treatment of **11** with acetaldehyde in the presence of DABCO resulted in a product that had lost the oxazolidinone. The formation of lactones such as this (incorporating two equivalents of aldehyde) had been noted only once previously with little asymmetric induction.[13] We were able to examine the lactones prepared from the oxazolidinone via chiral GC analysis and found that our result was not much of an improvement. We decided to look at alternative auxiliaries such as the Curran-Rebek imide (**13**),[14] but were unable to improve on our original findings. Finally, in order to be thorough, we examined the viability of Oppolzer's sultam (**14**) in this reaction.[15] This auxiliary had previously been reported to lead only to dimerization products,[16] so we were delighted to find that the reaction proceeded to give the same lactone products we had previously obtained. Chiral GC analysis revealed that the products had been obtained with outstanding stereocontrol, as only a single enantiomer could be detected. It is noteworthy that the sultam auxiliary is automatically expelled under the reaction conditions and is recovered in the purification of the lactone adducts. In this sense, it can be recycled without any additional effort. Furthermore, since it is readily available (from camphor-

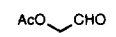
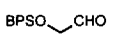
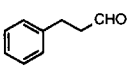
Scheme VI




sulfonic acid) in either enantiomeric form, Oppolzer's sultam is a very practical chiral auxiliary.[17] Extension to a variety of other aldehydes showed that it is also a very versatile auxiliary in the Baylis-Hillman reaction (Scheme VII). In every case studied, only a single enantiomer was observed, indicative of better than 99% enantiomeric excess. It should be pointed out that the reaction with isobutyraldehyde proceeded in poor yield to give **17**, and that benzaldehyde could not be made to serve as a substrate (*vide infra*).

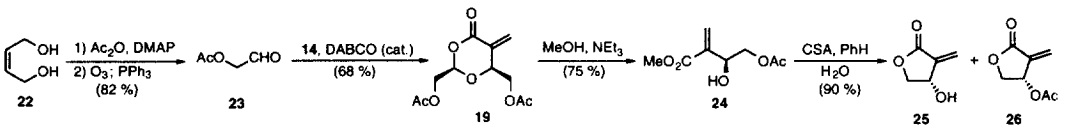
Scheme VII




| Aldehyde | yield | product |
|---|---|---|
|  | 98 % | **15** (R = Et) |
|  | 70 % | **16** (R = *n*-Pr) |
|  | 33 % | **17** (R = *i*-Pr) |
|  | 67 % | **18** (R = *i*-Bu) |
|  | 68 % | **19** (R = $AcOCH_2$) |
|  | 61 % | **20** (R = $BPSOCH_2$) |
|  | 0 % | |
|  | 68 % | **21** (R = $PhCH_2CH_2$) |

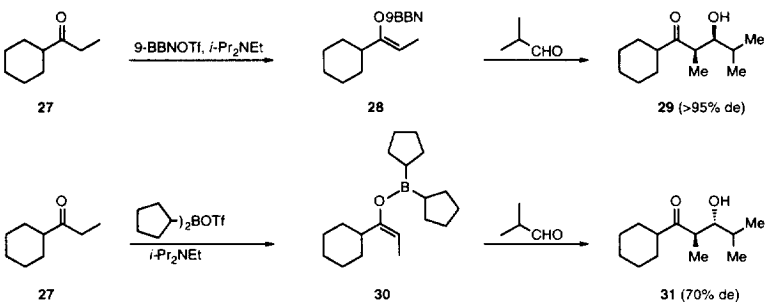
In order to ascertain the sense of asymmetric induction in the aforementioned Baylis-Hillman reaction, we turned our attention to the total synthesis of tulipalin B (**25**, Scheme VIII).[18] This lactone is a contact dermatitic agent isolated with glycosylated congeners from tulip bulbs, and has previously been prepared from (*S*)-malic acid.[19] Addition of **14** to aldehyde **23**[20] (available from 2-buten-1,4-diol via standard protocol) gave exclusively **19**. Methanolysis of the lactone followed by further treatment with acid provided synthetic tulipalin B (with some acetate protected tulipalin B (**26**)) in excellent agreement with the known material.

Scheme VIII



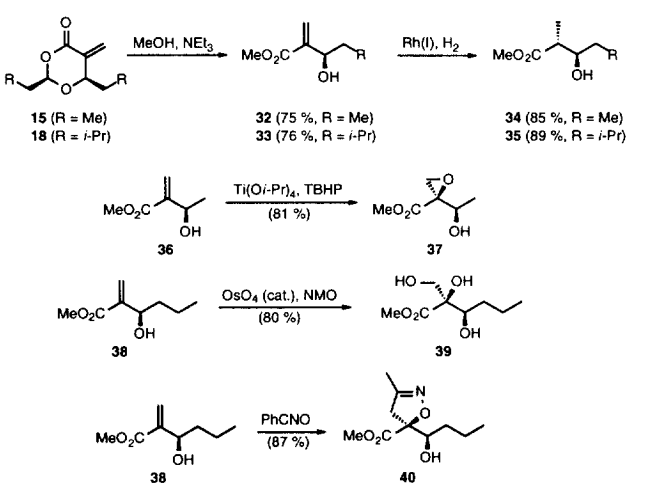
One of the goals of our efforts into the Baylis-Hillman reaction was to devise a method for the generation of polypropionates that have heretofore been difficult to prepare in a selective manner. The preponderance of polypropionates in nature has prompted a tremendous amount of work aimed at their synthesis in isomerically pure form.[21] Prominent among this work has been the study of aldol additions.[22] The addition of enolates to aldehydes is a carbon-carbon bond forming process that could produce two different diastereomeric products (syn **28** or anti **30**, Scheme IX), and these typically arise from the corresponding *Z*- or *E*-enolates. Although the use of *Z*-enolates in the generation of syn aldol adducts has been quite profitable, the corresponding reaction with *E*-enolates often gives a mixture of diastereomers.[23]

Scheme IX



With an asymmetric source of Baylis-Hillman products in hand, we were prepared to examine the possibility that they could serve as propionate surrogates (Scheme X). Toward this end, the lactones formed in the

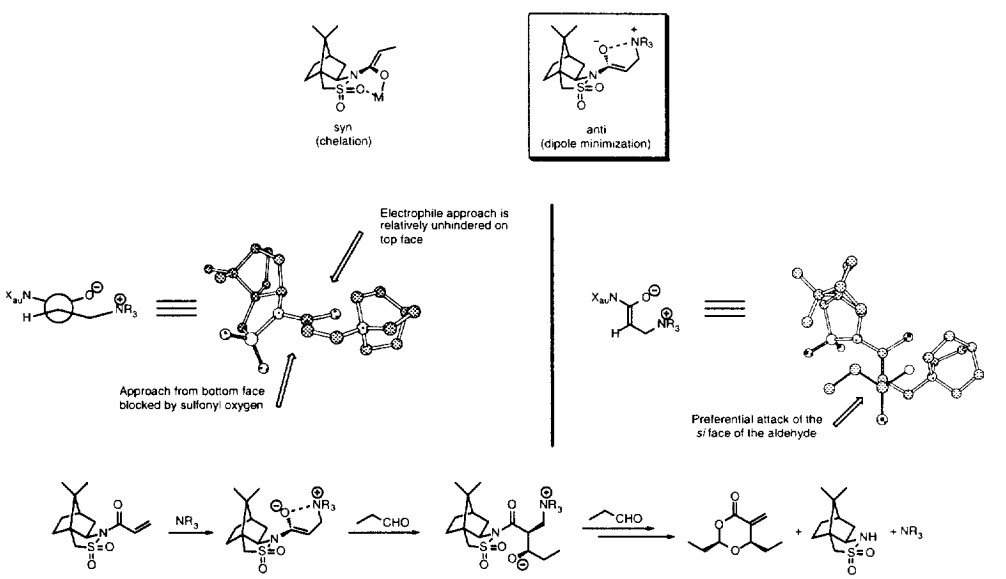
Scheme X



Baylis-Hillman reaction could be easily opened with methanol to give the α-methylene-β-hydroxyesters. These compounds serve as a useful template for the enantiospecific preparation of a variety of compounds.[3] Directed aziridinations,[24] epoxidations[25] and dihydroxylations[26] have already been demonstrated on Baylis-Hillman adducts, and dipolar cycloadditions have also been performed with good stereoselectivity.[27] For the purposes of preparing anti aldol adducts, we were interested in the directed reduction of these optically pure products.[28] Directed delivery of hydrogen to the acrylate proceeds with excellent stereoselectivity and results in the formation of an anti aldol equivalent. Since the starting materials were prepared in high enantiomeric excess, the net result is an enantiospecific method for the preparation of anti aldol adducts, and comparison with known compounds prepared independently helped confirm the sense of asymmetric induction in the initial Baylis-Hillman reaction.

With incontrovertible evidence that the reaction had proceeded with high and predictable stereocontrol, we were interested in understanding the nature of asymmetric induction. Since Oppolzer's sultam is such a well studied auxiliary,[29] we were able to glean useful information from the literature. The sultam is similar to a chemical chameleon in that the conditions used in a particular reaction can reverse the stereochemical outcome. When the sultam is used in conjunction with a coordinating Lewis acid, the pseudoequatorial sulfonyl oxygen and the imide oxygen maintain a syn relationship about the imide linkage due to chelation effects (Scheme XI).[30] In the absence of such a coordinating species, however, these oxygens adopt an anti relationship in order to minimize the relative dipole effects of the two electronegative oxygen substituents.[31] Therefore, the sense of asymmetric induction is thus dictated by the absence or presence of a coordinating species. In the case of the Baylis-Hillman reaction, the quaternary ammonium group is the only cationic entity, ruling out the syn (chelated) pathway. Further consideration of the nucleophilic attack of an electrophile with the resultant enolate indicates that the electrophile must approach from the *re* face (the "top" face as drawn in Scheme XI) or the *si* face of the enolate. Using Curran's model for bornane sultams,[32] the Newman projection along the enolate bond indicates a preference for electrophiles to approach from the top (*re*) face in order to avoid unfavorable

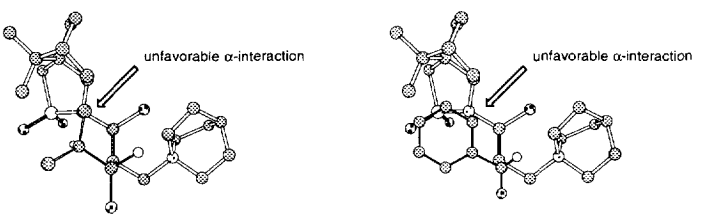
Scheme XI



interaction with the pseudoaxial sulfonyl oxygen that projects toward the bottom (*si*) face.[33] It is noteworthy that the methyl substituents on the bridging methylene of the norbornane skeleton do not appear to be in close proximity to the site of addtion in this reaction.[32] The stereochemical outcome at the β-position can also be explained from Curran's model. The lack of a coordinating metal in the Baylis-Hillman case dictates that the reaction is proceeding via an open transition state aldol addition.[22] The approach of the aldehyde is predicted to occur from the *si* face of the aldehyde, as this would project the alkyl substituent over the relatively small pseudoequatorial oxygen as opposed to the ionic isoxazoline ring. Note that the chiral auxiliary apparently occupies a position relatively remote from the enolate carbon and allows for this selective attack. The result is the selective formation of a syn aldol adduct intermediate, which incorporates a second equivalent of aldehyde and yields the lactone along with Oppolzer's sultam and the amine catalyst.

This model also explains some of the shortcomings we have discovered from the study of Oppolzer's sultam in the Baylis-Hillman reaction. Specifically, α-branched aldehydes have not been good substrates for this methodology. As noted above, isobutyraldehyde proceeds in low yield, which would be predicted from the same model proposed above (Scheme XII). The fact that the α-center can still adopt an orientation with the proton projected toward the sultam probably accounts for the observed formation of product. Benzaldehyde, which cannot adopt such an orientation, has not been found to serve as a substrate to date, and pivaldehyde also does not undergo Baylis-Hillman addition with **14**.

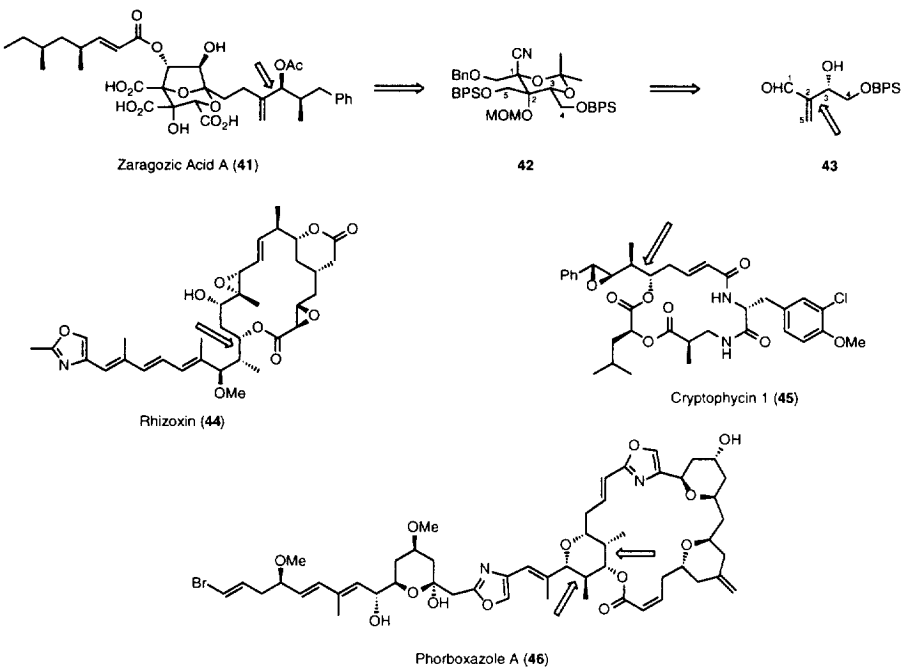
Scheme XII




With a reliable method for the generation of Baylis-Hillman adducts with high enantiomeric purity, we have begun to examine the prospects of using this reaction in the synthesis of natural product targets. Zaragozic acid A (**41**, Scheme XIII),[34] a fungal metabolite that exhibits potent hypocholesterolemic activity, was the first target examined from this vantage point.[35] Disconnections can be seen in both the natural product target and in a potential starting point (**43**).

The ability to perform directed reductions on Baylis-Hillman products to provide anti aldol equivalents has allowed us to consider these intermediates in the syntheses of several other active targets in our group. The total synthesis of rhizoxin (**44**),[36] an antitumor macrolide from the fungus *Rhizopus chinensis*, is currently being pursued,[37] as are syntheses of cryptophycin 1 (**45**)[38] and phorboxazole A (**46**).[39] The former is a subpicomolar in vivo antitumor macrolide isolated from a deep sea cyanobacterium, while the latter alkaloid, isolated from the marine sponge *Phorbas* sp., exhibits potent cytostatic activity. Progress towards these goals will be reported in due course.

Scheme XIII

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## Experimental Section

**General.** Unless otherwise noted, all compounds were obtained from Aldrich Chemical Company and were used without further purification. Dichloromethane was distilled from calcium hydride under nitrogen. Anhydrous methanol was distilled from magnesium turnings and iodine. Triethylamine was distilled and stored over potassium hydroxide. Unless otherwise indicated, organic extracts were dried over magnesium sulfate. Analytical thin-layer chromatography was performed with E. Merck 250-mm precoated F-254 silica gel 60 plates. Flash chromatography[40] was run under air pressure using 230 - 400 mesh silica gel supplied by E. Merck (Darmstadt). $^1H$ and $^{13}C$ NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ except where noted and coupling constants are reported in Hz. Infrared spectra were recorded as neat films on sodium chloride plates. Enantiomeric excess was determined via gas chromatography using a cyclodextrin B column (30 m x 0.32 μm id) with head pressure set at 20 psi and a temperature program of 70 °C for 5 min followed by a 4 °C/min ramp. Microanalyses were performed by MHW Laboratories, Phoenix, AZ.

**Methyl 4-*tert*-butyldiphenylsilyloxy-3-hydroxy-2-methylenebutanoate (5).** To the neat aldehyde **4**[41] (1.3817 g, 4.63 mmol) was added DABCO (0.1633 g, 1.3 mmol) and methyl acrylate (2.5 mL, 27.7 mmol). The mixture was allowed to stir at rt for 30 d. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography to afford **5** (0.7157 g, 40 %) as a colorless oil. bp 150 °C at 0.15 mm Hg. IR 3550, 2960, 2940, 2860, 1720, 1120 $cm^{-1}$. $^1H$ NMR (500 MHz) δ 1.07 (s, 9), 3.08 (d, 1, $J$ = 5.5), 3.61 (dd, 1, $J$ = 10.2, 3.9), 3.68 (s, 3), 3.92 (dd, 1, $J$ = 10.1, 4.1), 4.65 (m, 1), 6.00 (s, 1), 6.37 (s, 1), 7.41 (m, 6), 7.66 (m, 4). $^{13}C$ NMR (125 MHz) δ 19.2, 26.7, 51.6, 67.0, 70.9, 126.6, 127.7, 129.7, 132.9, 135.5, 139.0, 166.2. Anal. Calcd. for $C_{22}H_{28}O_4Si$: C 68.72, H 7.34. Found: C 68.67, H 7.47.

**Methyl 3-hydroxy-2-methylenepentanoate (7).**[42] **DABCO catalysis:** To a solution of propionaldehyde (**6**) (24.7 mL, 0.342 mol) and methyl acrylate (18.3 mL, 0.203 mol) in dichloromethane (25 mL) was added DABCO (1.0 g, 8.9 mmol). The solution was stirred at rt for 10 d, then diluted with dichloromethane (250 mL) and washed with 1 N HCl. The organic layer was then dried and concentrated under reduced pressure. Purification by flash chromatography afforded **7** (24.68 g, 84 %) as a colorless oil. IR 3440, 2980, 1720, 1130 $cm^{-1}$. $^1H$ NMR δ d 0.90 (t, 3, $J$ = 6.5), 1.64 (m, 2), 2.90 (br s, 1), 3.75 (s, 3), 4.32 (t, 1, $J$ = 6.3), 5.75 (s, 1), 6.19 (s, 1). $^{13}C$ NMR δ 15.8, 22.3, 50.8, 68.6, 124.8, 144.1, 166.7.

**Methyl 3-hydroxy-2-methylenepentanoate (7).**[42] **$PBu_3$ catalysis:** To a solution of propionaldehyde (10.0 mL, 0.139 mol) and methyl acrylate (7.5 mL, 83.3 mmol) in dichloromethane (15 mL) was added tributylphosphine (1.0 g, 4.9 mmol). The solution was stirred at rt for 2 d, then concentrated under reduced pressure. Purification by flash chromatography afforded **7** (9.59 g, 80 %) as a colorless oil.

**Methyl 3-hydroxy-2-methylenepentanoate (7).**[42] **Low temperature:** A solution of propionaldehyde (6.5 mL, 90.1 mmol) and methyl acrylate (5.0 mL, 55.5 mmol) in dichloromethane (25 mL) was cooled to 0 °C and DABCO (0.5 g, 4.4 mmol) was added. The solution was stirred at 0 °C for 8 h, then concentrated cold under reduced pressure. Purification by flash chromatography afforded **7** (5.69 g, 71 %) as a colorless oil.

***(R)* Methyl 3-hydroxy-2-methylenebutyrate (10).**[43] A mixture of (*R*)-(–)-3-hydroxyquinuclidine[44] (72.0 mg, 0.57 mmol) methyl acrylate (2.0 mL, 24 mmol) and acetaldehyde (0.20 mL, 3.6 mmol) in dichloromethane (2 mL) was stirred overnight at rt. The mixture was concentrated under reduced pressure and purified by flash chromatography to give **10** (450 mg, 96 %) as a colorless oil. $[\alpha]_D$ = + 0.1 ($c$ = 9.0, $CHCl_3$). $^1H$ NMR δ 1.39 (d, 3, $J$ = 6.5), 2.76 (d, 1, $J$ = 5.6), 3.79 (s, 3), 4.60 (m, 1), 5.84 (t, 1, $J$ = 1.1), 6.22 (d, 1, $J$ = 0.6).

**2(*S*), 6(*S*)-2,6-Dimethyl-5-methylene-1,3-dioxan-4-one ((–)-12).** A stirred solution of acrylate **11**[31] (149.9 mg, 0.6 mmol) in dichloromethane (2 mL) was cooled to 0 °C and acetaldehyde (2.0 mL, 36 mmol) was added followed by DABCO (31 mg, 0.28 mmol). The solution was stirred at 0 °C for 12 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography to provide(–) **12** (62.5 mg, 73 %) as a colorless oil. $[\alpha]_D$ = – 9.6 ($c$ = 1.5, $CHCl_3$). IR 2965, 1725, 1630, 1465, 1410, 1285, 1200 $cm^{-1}$. $^1H$ NMR (500 MHz) δ 1.47 (d, 3, $J$ = 6.3), 1.50 (d, 3, $J$ = 5.1), 4.64 (m, 1), 5.50 (q, 1, $J$ = 5.1), 5.60 (d, 1, $J$ = 2.4), 6.50 (d, 1, $J$ = 2.4). $^{13}C$ NMR (125 MHz) δ 20.3, 20.9, 34.4, 99.5, 125.5, 137.7, 163.2. Anal. Calcd. for $C_7H_{10}O_3$: C 59.14, H 7.09. Found: C 58.74, H 7.40.

**2(*R*), 6(*R*)-2,6-Dimethyl-5-methylene-1,3-dioxan-4-one (12).** A stirred solution of acrylate **14**[45] (1.00 g, 3.7 mmol) in dichloromethane (5 mL) was cooled to 0 °C and acetaldehyde (2.38 g, 54 mmol) was added followed by DABCO (0.27 g, 1.85 mmol). The solution was stirred at 0 °C for 8 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography to provide **12** (448 mg, 85 %) as a colorless oil. $[\alpha]_D$ = + 73.4 ($c$ = 1.8, $CHCl_3$).

**2(*R*), 6(*R*)-2,6-Diethyl-5-methylene-1,3-dioxan-4-one (15).** Following the procedure described above with propionaldehyde, **15** was obtained as a colorless oil (98 %). $[\alpha]_D$ = + 70.2 ($c$ = 1.0, $CHCl_3$). $^1H$ NMR δ 0.85 (t, 6, $J$ = 6.9), 1.55 (m, 2), 1.76 (m, 2), 4.43 (m, 1), 5.15 (t, 1, $J$ = 5.3), 5.52 (d, 1, $J$ = 2.2), 6.38 (d, 1, $J$ = 2.3). $^{13}C$ NMR δ 13.4, 15.6, 34.2, 35.3, 78.1, 100.5, 124.9, 137.7, 163.5.

**2(*R*), 6(*R*)-2,6-Dipropyl-5-methylene-1,3-dioxan-4-one (16).** Following the procedure described above with butyraldehyde, **16** was obtained as a colorless oil (70 %). $[\alpha]_D$ = + 87.2 ($c$ = 1.1, $CHCl_3$). IR 2970, 2720, 1720, 1630, 1440, 1390, 1280 $cm^{-1}$. $^1H$ NMR (500 MHz) δ 0.92 (t, 6, $J$ = 7.5), 1.46 (m, 4), 1.69 (m, 4), 5.50 (m, 1), 5.28 (t, 1, $J$ = 5.2), 5.55 (d, 1, $J$ = 2.1), 6.42 (d, 1, $J$ = 2.4). $^{13}C$ NMR (125 MHz) δ 13.6, 13.7, 16.4, 17.8, 36.3, 36.9, 77.3, 101.8, 125.0, 137.2, 163.9. Anal. Calcd. for $C_{11}H_{18}O_3$: C 66.64, H 9.15. Found: C 66.38, H 9.51.

**2(*R*), 6(*R*)-2,6-Di-isopropyl-5-methylene-1,3-dioxan-4-one (17).** Following the procedure described above with isobutyraldehyde, **17** was obtained as a colorless oil (33 %). $[\alpha]_D$ = + 42.7 ($c$ = 0.9, $CHCl_3$). $^1H$

NMR (300 MHz) δ 0.93 (m, 12), 1.40 (m, 2), 4.57 (m, 1), 5.02 (d, 1, $J$ = 6.5), 5.50 (d, 1, $J$ = 2.0), 6.42 (d, 1, $J$ = 2.0).

**2(*R*), 6(*R*)-2,6-Di-isobutyl-5-methylene-1,3-dioxan-4-one (18).** Following the procedure described above with isovaleraldehyde, **18** was obtained as a colorless oil (67 %). $[\alpha]_D$ = + 59.8 ($c$ = 7.5, $CHCl_3$). $^1$H NMR δ 0.88 (m, 12), 1.50 (m, 2), 1.72 (m, 2), 1.91 (m, 2), 4.58 (m, 1), 5.35 (t, 1, $J$ = 6.3), 5.59 (d, 1, $J$ = 1.8), 6.46 (d, 1, $J$ = 1.9). $^{13}$C NMR δ 13.4, 13.6, 13.7, 13.8, 28.4, 29.5, 34.1, 35.2, 78.5, 101.2, 124.6, 138.2, 164.1.

**2(*R*), 6(*S*)-2,6-Di-(acetoxymethyl)-5-methylene-1,3-dioxan-4-one (19).** Following the procedure described above with acetoxyacetaldehyde (**23**),[23] **19** was obtained as a colorless oil (68 %). $[\alpha]_D$ = + 80.0 ($c$ = 1.2, $CHCl_3$). IR 2925, 2855, 1740, 1625, 1460, 1375 cm$^{-1}$. $^1$H NMR (500 MHz) δ 2.10 (s, 3), 2.12 (s, 3), 4.29 (d, 2, $J$ = 4.5), 4.31 (d, 1, $J$ = 5.8), 4.38 (dd, 1, $J$ = 12.1, 3.3), 4.92 (m, 1), 5.54 (t, 1, $J$ = 4.5), 5.79 (d, 1, $J$ = 2.1), 6.59 (d, 1, $J$ = 2.4). $^{13}$C NMR (125 MHz) δ 20.5, 20.6, 63.3, 65.2, 75.7, 94.7, 127.9, 132.6, 162.1, 170.2, 170.5. Anal. Calcd. for $C_{11}H_{14}O_7$: C 51.16, H 5.46. Found: C 51.41, H 5.67.

**2(*R*), 6(*S*)-2,6-Di-(*tert*-butyldiphenylsilyloxymethyl)-5-methylene-1,3-dioxan-4-one (20).** Following the procedure described above with **4**, **20** was obtained as a colorless oil (61 %). $[\alpha]_D$ = + 70.2 ($c$ = 2.0, $CHCl_3$). $^1$H NMR δ 1.07 (s, 9), 1.09 (s, 9), 4.14 (d, 2, $J$ = 4.7), 4.24 (d, 2, 4.4), 5.03 (m, 1), 5.49 (t, 1, $J$ = 4.6), 5.80 (d, 1, $J$ = 2.2), 6.61 (d, 1, $J$ = 2.2), 7.45 (m, 12), 7.67 (m, 8).

**2(*R*), 6(*R*)-2,6-Di-(2-phenylethyl)-5-methylene-1,3-dioxan-4-one (21).** Following the procedure described above with hydrocinnamaldehyde, **21** was obtained as a colorless oil (68 %). $[\alpha]_D$ = + 47.2 ($c$ = 1.1, $CHCl_3$). IR 2930, 2865, 1740, 1630, 1605, 1495, 1455 cm$^{-1}$. $^1$H NMR δ 2.12 (m, 4), 2.82 (m, 4), 5.51 (m, 1), 5.30 (t, 1, $J$ = 5.1), 5.60 (d, 1, $J$ = 2.2, 6.51 (d, 1, $J$ = 2.4), 7.15 (m, 10). $^{13}$C NMR δ 29.3, 30.7, 35.8, 36.6, 76.5, 101.0, 125.6, 126.2, 128.4, 128.4, 128.5, 128.5, 136.8, 136.8, 140.5, 140.9, 163.6. Anal. Calcd. for $C_{21}H_{22}O_3$: C 78.23, H 6.88. Found: C 78.57, H 7.21.

**Acetoxyacetaldehyde (23).**[20] To a solution of 2-butene-1,4-diol (1.5325 g, 17.4 mmol) in dichloromethane (100 mL) was added triethylamine (7 mL, 50 mmol) and DMAP (0.2066 g, 1.7 mmol). The solution was cooled to 0 °C and acetic anhydride (4.0 mL, 42 mmol) was added. The solution was allowed to warm to rt overnight and saturated sodium bicarbonate (40 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated sodium chloride, dried and concentrated under reduced pressure to give 1,4-diacetoxy-2-butene (2.8970 g, 97 %) as a colorless oil. IR 2955, 1740, 1650, 1455, 1375, 1230, 1030, 975 cm$^{-1}$. $^1$H NMR δ 2.05 (s, 6), 4.66 (d, 2, $J$ = 5.2), 5.73 (tt, 4, $J$ = 5.2, 1.2). $^{13}$C NMR δ 20.8, 60.0, 128.0, 170.6. Anal. Calcd. for $C_8H_{12}O_4$: C 55.81, H 7.02. Found: C 56.00, H 6.86.

A solution of 1,4-diacetoxy-2-butene (4.3092 g, 25.0 mmol) in dichloromethane (200 mL) was cooled to – 78 °C. Ozone was bubbled through the solution until it turned blue, then nitrogen was bubbled through the solution until the blue color disappeared. To this cold solution was added triphenylphosphine (8.0 g, 30 mmol) and the mixture was allowed to warm slowly to rt. The solution was then concentrated under reduced pressure to give a white solid that was purified by flash chromatography to yield **23** (4.2917 g, 84 %) as a colorless oil. bp 65-70 °C at 13 mm Hg. IR 2940, 2845, 2730, 1730, 1420, 1375, 1230, 1130, 1085, 1050, 960 cm$^{-1}$. $^1$H NMR δ 2.20 (s, 3), 4.68 (s, 2), 9.60 (s, 1). $^{13}$C NMR δ 20.3, 68.6, 170.3, 195.6. Anal. Calcd. for $C_4H_6O_3$: C 47.06, H 5.92. Found: C 46.90, H 5.97.

**(*S*) Methyl 4-acetoxy-3-hydroxy-2-methylenebutanoate (24).** A solution of acrylate **19** (521 mg, 2.0 mmol) and triethylamine (0.1 mL) in anhydrous methanol (30 mL) was warmed to 45 °C for 10 min, then concentrated under reduced pressure in a warm water bath. The resulting residue was purified by flash column chromatography to yield **24** (283 mg, 75 %) as a colorless oil. $[\alpha]_D$ = + 25.0 ($c$ = 2.4, $CHCl_3$). IR 3470, 2955, 1725, 1630, 1440, 1380, 1160 cm$^{-1}$. $^1$H NMR δ 2.10 (s, 3), 3.81 (s, 3), 4.20 (dd, 1, $J$ = 11.5, 6.9), 4.31 (dd, 1, $J$ = 11.5, 3.6), 4.74 (m, 1), 6.00 (d, 1, $J$ = 1.1), 6.40 (d, 1, $J$ = 0.8). $^{13}$C NMR δ 20.8, 52.0, 67.4, 69.7, 127.3, 128.3, 138.5, 166.2, 171.3. Anal. Calcd. for $C_8H_{12}O_5$: C 51.06, H 6.43. Found: C 50.92, H 6.37.

**Tulipalin B (25) and acetyltulipalin B (26).** A solution of **24** (247.2 mg, 1.3 mmol) in toluene (55 mL) containing water (0.1 mL) and camphorsulfonic acid (62 mg) was heated to reflux for 5 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography to give **25** (38.0 mg, 25 %) and **26** (132.5 mg, 65%) as colorless oils. **Data for 25:** $[\alpha]_D$ = – 86.0 ($c$ = 0.9, $CHCl_3$) [lit.[46] $[\alpha]_D$ = – 82.0 ($c$ = 1, $CHCl_3$). IR 3420, 2975, 2910, 1755, 1670, 1415, 1275 cm$^{-1}$. $^1$H NMR (500 MHz) δ 2.93 (br s, 1), 4.18 (dd, 1, $J$ = 10.0, 3.6), 4.50 (dd, 1, $J$ = 10.1, 6.6), 4.95 (t, 1, $J$ = 2.1), 6.02 (d, 1, $J$ = 1.7), 6.42 (d, 1, $J$ = 2.0). $^{13}$C NMR (125 MHz) δ 67.5, 73.5, 126.8, 137.6, 169.8. Anal. Calcd. for $C_5H_6O_3$: C 52.63, H 5.30. Found: C

52.41, H 5.47. **Data for 26:** $[\alpha]_D = -29.1$ ($c = 1.8$, $CHCl_3$). IR 3105, 2975, 1765, 1670, 1410, 1375 $cm^{-1}$. $^1H$ NMR δ 2.12 (s, 3), 4.30 (dd, 1, $J = 10.9, 2.5$), 4.59 (dd, 1, $J = 10.9, 6.4$), 5.82 (m, 1), 6.15 (d, 1, $J = 1.5$), 6.55 (d, 1, $J = 1.8$). $^{13}C$ NMR δ 20.8, 68.9, 70.6, 129.8, 133.3, 168.2, 170.4. Anal. Calcd. for $C_7H_8O_4$: C 53.85, H 5.16. Found: C 54.01, H 5.15.

**(*R*) Methyl 3-hydroxy-2-methylenepentanoate (32).** A solution of acrylate **15** (1.00 g, 5.9 mmol) in anhydrous methanol (20 mL) was cooled to 0 °C and camphorsulfonic acid (2.6 mg) was added. The solution was stirred at 0 °C for 40 min and triethylamine (2 drops) was added. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography to give **32** (638 mg, 75 %) as a colorless oil. $[\alpha]_D = +7.7$ ($c = 0.5$, $CHCl_3$). $^1H$ NMR δ 0.90 (t, 3, $J = 6.5$), 1.64 (m, 2), 2.90 (br. s, 1), 3.75 (s, 3), 4.32 (t, 1, $J = 6.3$), 5.75 (s, 1), 6.19 (s, 1). $^{13}C$ NMR δ 15.8, 22.3, 50.8, 68.6, 124.8, 144.1, 166.7.

**(*R*) Methyl 3-hydroxy-5-methyl-2-methylenehexanoate (33).** Following the procedure described above with **18**, **33** (76 %) was obtained as a colorless oil. $[\alpha]_D = +21.8$ ($c = 4.0$, $CHCl_3$). $^1H$ NMR δ 0.86 (m, 6), 1.38 (m, 2), 1.75 (m, 1), 3.75 (s, 3), 4.40 (m, 1), 5.77 (d, 1, $J = 1.6$), 6.12 (d, 1, $J = 1.7$). $^{13}C$ NMR δ 13.8, 14.2, 28.1, 30.4, 50.7, 67.7, 125.1, 166.8.

**2(*R*), 3(*R*) Methyl 3-hydroxy-2-methylpentanoate (34).**[47] A solution of acrylate **32** (0.100 g, 0.69 mmol) in anhydrous methanol (15 mL) was degassed and [Rh(nbd)(diphos-4)]$BF_4$[48] (26.0 mg, 5 mol %) was added under a nitrogen atmosphere. The solution was then stirred under an atmosphere of hydrogen until the consumption of starting material was complete by thin layer chromatography (approximately 2 h). The solution was then concentrated under reduced pressure and triturated with a mixture of ether/petroleum ether (1:3). The mixture was filtered through a plug of silica gel and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford **34** (86.1 mg, 85 %) as a colorless oil. $[\alpha]_D = -9.7$ ($c = 1.1$, $CHCl_3$) [lit. $[\alpha]_D = -9.9$ ($c = 1.28$, $CHCl_3$). $^1H$ NMR δ 0.91 (t, 3, $J = 7.1$), 1.12 (d, 3, $J = 6.9$), 1.36 (m, 1), 1.50 (m, 1), 2.46 (quin, 1, $J = 6.1$), 2.65 (br. s, 1), 3.52 (m, 1), 3.62 (s, 3).

**2(*R*), 3(*R*) Methyl 2,5-dimethyl-3-hydroxypentanoate (35).**[49] A solution of acrylate **33** (0.100 g, 0.58 mmol) in anhydrous methanol (10 mL) was degassed and [Rh(nbd)(diphos-4)]$BF_4$ (20 mg, 5 mol %) was added under a nitrogen atmosphere. The solution was then stirred under an atmosphere of hydrogen until the consumption of starting material was complete by thin layer chromatography. The solution was then concentrated under reduced pressure and triturated with a mixture of ether/petroleum ether (1:3). The mixture was filtered through a plug of silica gel and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford **35** (90.4 mg, 89 %) as a colorless oil. $[\alpha]_D = -9.2$ ($c = 4.0$, $CHCl_3$). $^1H$ NMR δ 0.85 (t, 6, $J = 6.7$), 1.12 (d, 3, $J = 6.7$), 1.16 (m, 2), 1.30 (m, 1), 1.80 (m, 1), 3.63 (s, 3), 3.65 (m, 1).

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