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The first practical approach to optically pure cyclopropanes derived from *trans* γ-hydroxy enones

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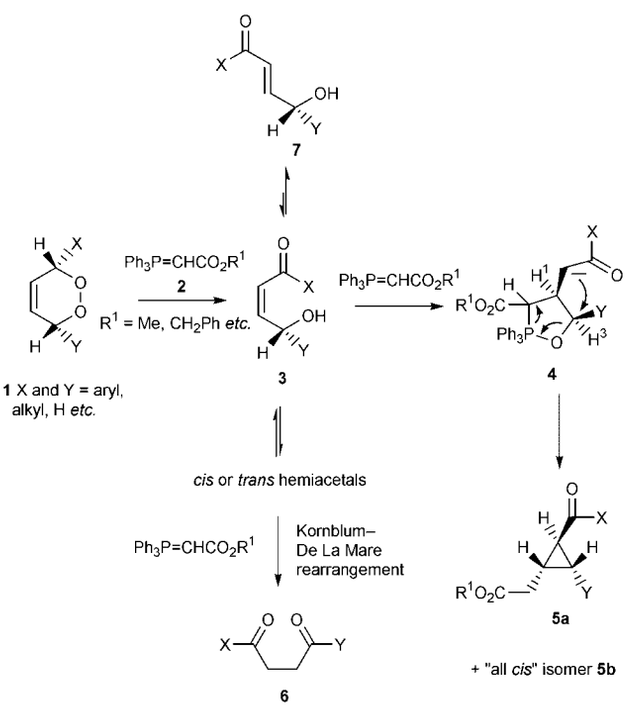
A new approach for the synthesis of optically pure cyclopropanes from *trans* γ-hydroxy enones and stabilised phosphorus ylides is presented; the use of light and a triplet sensitiser leads to a dramatic increase in reaction rate and isolated yield.

The most noticeable current strategies for the construction of the cyclopropyl motif include, i) the direct carbene transfer (both stoichiometric and catalytic) from a diazo precursor to an olefin utilising transition metals (Rh, Cu, Zn and Pd)[1] and ii) Michael addition of nucleophiles (usually sulfur ylides) to α,β-unsaturated ketones and esters followed by intramolecular cyclisation.[2] Despite the great advances in these areas, the efficient synthesis of diversely functionalised enantiopure cyclopropanes containing greater than di-substitution still remains a considerable challenge. We recently reported on a new approach to diastereomerically pure diversely functionalised cyclopropanes **5a** which utilised 1,2-dioxines **1** and stabilised phosphorus ester ylides as the key precursors (Scheme 1).[3] Key features of the cyclopropanation sequence



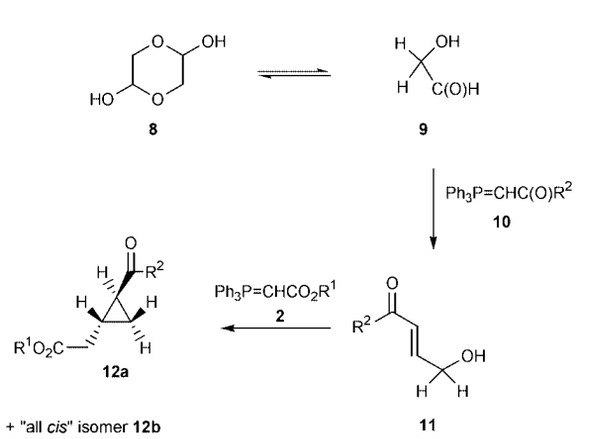
Scheme 1

included the ylide acting as a mild base inducing ring opening of the 1,2-dioxines **1** to their isomeric *cis* γ-hydroxy enones **3**, Michael addition of the ylide to the *cis* γ-hydroxy enones **3** and attachment of the electrophilic phosphorus pole of the ylide to the hydroxy moiety afford the intermediate 1,2λ^5-oxaphospholanes **4** and sets up the observed *cis* stereochemistry between H1 and H3. Cyclisation of the resultant enolate, expulsion of triphenylphosphine oxide and proton transfer from the reaction manifold afford the observed cyclopropanes in excellent diastereomeric excess. A minor amount of the "all *cis*" isomer **5b** is occasionally formed. While cyclopropanation is favored by the use of ester stabilised ylides **2**, the use of keto or aldo stabilised ylides results in a preference for 1,4-dicarbonyl **6** formation through a competing Kornblum–De La Mare rearrangement of the intermediate hemiacetals.[4] The *trans* γ-hydroxy enones **7** were also shown to be a possible entry point into the cyclopropanation manifold, however, reaction times were excessive (weeks at ambient temp.) and yields were poor due to the position of the *cis–trans* equilibrium favoring the *trans* form.

According to Scheme 1, in order to allow for the preparation of enantiomerically pure cyclopropanes one would need to prepare either the *cis* or *trans* γ-hydroxy enones in an optically pure form. Synthesis of optically pure *cis* γ-hydroxy enones is unattractive as they are highly sensitive to acid and base, rearranging rapidly to furan or 1,4-diketone **6** respectively.[3] Therefore, we decided to embark on developing a practical strategy for the synthesis of optically pure *trans* γ-hydroxy enones **7**, which could be utilised for the construction of optically pure cyclopropanes. Additionally, we report herein the first practical approach to the shifting of the *cis–trans* γ-hydroxy enone equilibrium which allows for a dramatic acceleration in the rate of the cyclopropanation sequence along with an increase in overall yield.

Retrosynthetically, we envisaged that the *trans* γ-hydroxy enones **7** could be prepared from reaction of stabilised keto ylides on optically pure α-hydroxy aldehydes. The latter aldehydes themselves could be prepared from reduction of optically pure α-hydroxy esters. In order to test this general approach we first utilised the commercially available glycolaldehyde dimer **8**, which being optically inactive would result in the formation of only diastereomerically pure cyclopropanes (Scheme 2).†

Reaction of the glycolaldehyde dimer **8** with keto ylides **10** resulted in the smooth generation of the *trans* γ-hydroxy enones **11** which were judged to be of >90% purity by ^{1}H NMR. Direct



Scheme 2

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Table 1 Formation of cyclopropanes from glycolaldehyde dimer **8** under thermal and photolytic conditions[a]

			Thermal conditions		Photolytic conditions	
Entry	R^1	R^2	Cyclopropane (yield, %)	Time/h	Cyclopropane (yield, %)	Time/h
1	CH_2Ph	Ph	**12a** (35) **12b** (0)	120	**12a** (68) **12b** (0)	30
2	CH_3	Ph	—[b]	—	**12a** (64) **12b** (0)	30
3	CH_3	CH_3	**12a** (26) **12b** (6)	192	**12a** (41) **12b** (3)	96

[a] Yields quoted refer to isolated yields starting from **8**. The *trans* γ-hydroxy enones **11** were prepared under an inert atmosphere by heating a mixture of glycolaldehyde dimer **8** in CH_2Cl_2 (0.5 g in 32 mL) with ylide **10** (1.05 equiv.) under reflux. After 4 hours ylide **2** (1.5 equiv.) was then introduced and the mixture heated under reflux for the time indicated. The volatiles were then removed *in vacuo* and the residue subjected to column chromatography. The reactions performed under photolytic conditions were carried out in an identical manner except after the introduction of ylide **2**, the mixture was irradiated with light from 2 sun lamps (300 W) at a distance of 10 cm in the presence of benzophenone (10 mol%). [b] Complex mixture of unidentified products.

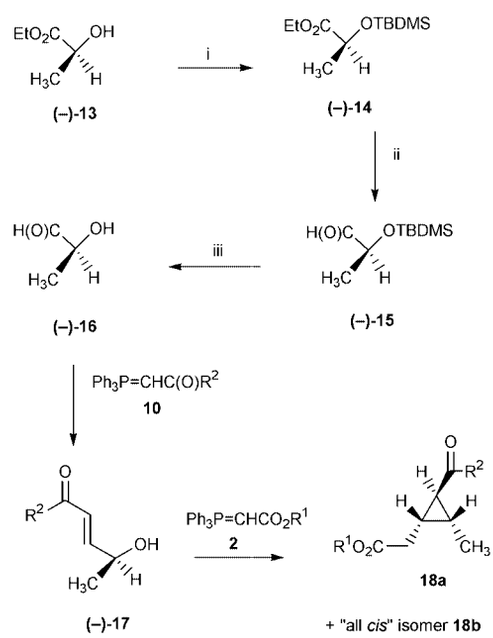
Table 2 Formation of enantiomerically pure cyclopropanes **18** from optically pure ethyl lactate **13**[a]

				Thermal conditions		Photolytic conditions	
Entry	R^1	R^2	Ent.[b]	Cyclopropane (yield, %)	Time/h	Cyclopropane (yield, %)	Time/h
1	CH_2Ph	Ph	−	**18a** (29) **18b** (4)	180	**18a** (50) **18b** (12)	40
2	CH_2Ph	Ph	+	**18a** (34) **18b** (2)	120	—[c]	—
3	CH_3	Ph	−	—[d]	—	**18a** (41) **18b** (9)	27
4	(−)-Menthol	Ph	−	—[c]	—	**18a** (40) **18b** (10)	27
5	CH_2Ph	*p*-Br-Ph	−	**18a** (48) **18b** (3)	144	**18a** (65) **18b** (6)	27
6	CH_2Ph	CH_3	−	**18a** (21) **18b** (0)	448	—[c]	—
7	CH_2Ph	*t*-Bu	−	**18a** (13) **18b** (5)	358	—[c]	—
8[e]	CH_2Ph	Ph	−	—[c]	—	**18a** (54) **18b** (8)	25

[a] Yields quoted refer to isolated yields starting from **16**. Time refers to overall reaction time. Both the *trans* γ-hydroxy enones **17** and the cyclopropanes **18** were prepared in an analogous manner to those described within Table 1 except the reaction time for enone formation was 5 hours. [b] Refers to the enantiomer of **13** utilised. [c] Not attempted. [d] Complex mixture of unidentified products. [e] DCA utilised as sensitiser.

addition of the ester stabilised ylides **2** to the reaction mixture resulted in the formation of the desired cyclopropanes **12** (entries 1–3, Table 1). Under thermal conditions the formation of the desired cyclopropanes was extremely slow due to the *cis–trans* γ-hydroxy enone equilibrium favouring the thermodynamically more stable *trans* isomers. Furthermore, the isolated yields were poor due to base induced Kornblum–De La Mare competing rearrangement of the resultant hemiacetals in solution and the formation of unidentified decomposition products. Previous studies showed that the cyclopropane yield is essentially quantitative when starting from the *cis* γ-hydroxy enones **3**.[3] Therefore, it seemed only reasonable to expect that if we could in some way shift the equilibrium away from the *trans* γ-hydroxy enones **11** and towards the *cis* γ-hydroxy enones, then we would expect an increase in overall cyclopropane yield coupled with an increase in reaction rate. Thus, we repeated the same three experiments in Table 1 under photolytic conditions utilising benzophenone as the sensitiser. As can be seen, not only did the yield of desired cyclopropane dramatically increase but also the overall reaction rate.

With the validity of this new approach to cyclopropane formation now established, we turned our attention to the preparation of optically pure cyclopropanes utilising optically pure α-hydroxy aldehydes (Scheme 3). Thus, protection of (−)-ethyl lactate **13** as the TBDMS ether proceeded in 89% yield. DIBAL-H reduction afforded aldehyde (−)-**15** in 81% yield which was deprotected with aqueous HF to afford (−)-**16**. This α-hydroxy aldehyde was immediately treated with keto ylides **10** to afford the intermediate optically pure *trans* γ-hydroxy enones (−)-**17**. Subsequent addition of ester ylides **2** gave rise to optically pure cyclopropanes, (Table 2) which were determined to be of >98% ee by ^{1}H NMR analysis in the presence of [Eu(hfc)$_3$].‡§ In a similar fashion, the opposite enantiomeric series (+)-**17** was prepared from (+)-methyl lactate. As can be seen by inspection of the data collated in Table 2, the yields are poor and reaction times excessive under thermal conditions. However, under photolytic conditions the overall reaction rate was once again dramatically accelerated, while the isolated yields of optically pure cyclopropanes were extremely good considering



Scheme 3 *Reagents and conditions*: i, TBDMSCl, imidazole (1.5 equiv.), DMF, 25 °C, 1.5 h, 98%; ii, DIBAL-H (1.5 equiv.), ether, −78 °C, 10 min, then MeOH–H_2O (dropwise) to 25 °C, 1 h, 81%; iii, aq. HF (48%), CH_3CN, 15 min, 82%.

they represent several synthetic transformations (*i.e.* **16** to **18**). Finally, we report that the use of benzophenone as the sensitiser in these reactions can be exchanged for dicyanoanthracene (DCA). While the use of DCA failed to dramatically increase cyclopropane yield, comparison of entries 1 and 8 within Table 2 reveals that it was effective in lowering the overall reaction time.

As the cyclopropanation can accommodate a wide range of substituents (*e.g.* H, alkyl and aryl) at the hydroxy terminus of the *trans* γ-hydroxy enones, we envisage that the approach

highlighted here will find application in the construction of a wide range of diversely functionalised optically pure cyclopropanes. We are currently evaluating the use of optically pure α-hydroxy aldehydes derived from ethyl mandelate and also from the sugar chiral pool which will be reported in due course along with a more thorough investigation of how other types of sensitisers influence the cyclopropanation sequence.

Acknowledgements

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Notes and references

† All new compounds have been fully characterised by elemental analysis, spectroscopy and mass spectrometry.
‡ (+)-Camphorate utilised.
§ hfc = tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

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