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Synthesis of Optically Active Cyclopenta[c]pyran-4-carboxylic Acid Derivatives, Building Blocks for Iridoids. An Attractive Alternative to Asymmetric de Mayo Reaction

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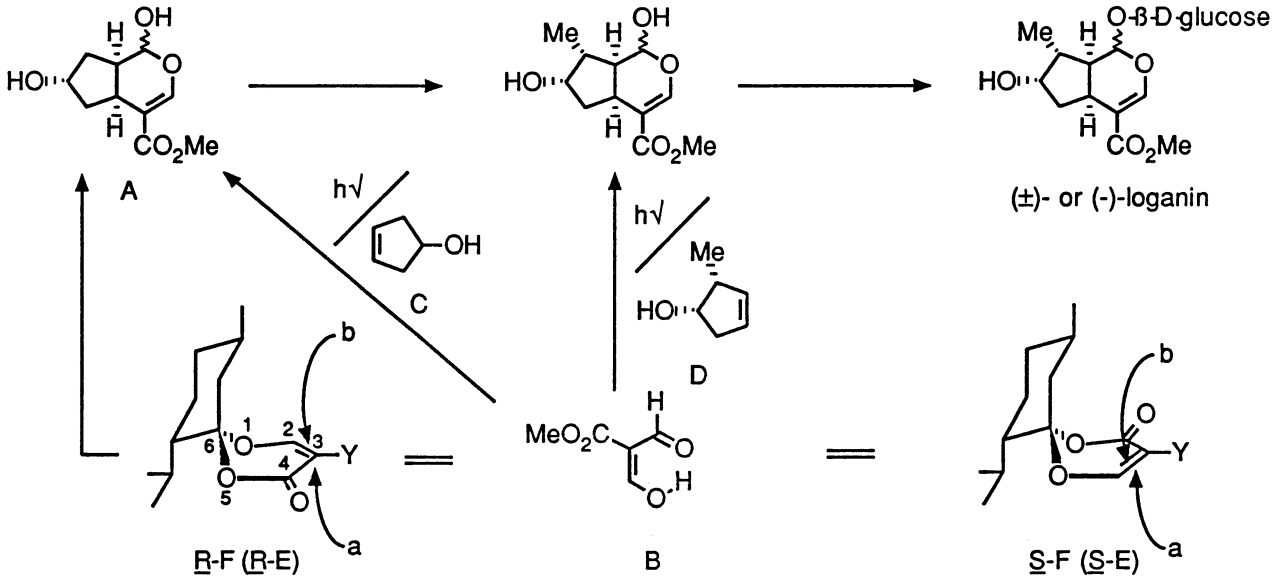
A new asymmetric de Mayo reaction leading to enantiomerically pure iridoids has been elaborated using chiral spirocyclic dioxinone as the photochemical equivalent of diformylacetate.

The functionalized cyclopenta[c]pyran-4-carboxylic acid derivative (**A**), an important building block for iridoids, such as (±)-loganin,[1] -sweroside,[2] and -secologanin,[2] has been synthesized for the first time by Büchi and then by Hutchinson et al. from methyl diformylacetate (**B**) as the enone and 3-cyclopentene-1-ol (**C**) as the enophile by an application of de Mayo reaction.[3] The fact that highly regio- and stereoselective transformations of **A** to (±)-loganin and related iridoids have been accomplished[1,2] indicates that **A** is a versatile synthon for iridoids in racemic series. While other methods are also available,[4-7] the enantioselective route to iridoids is to use chiral enophiles, e. g. (1S,2R)-2-methyl-3-cyclopenten-1-ol (**D**), in Büchi's method as exemplified in the synthesis of (+)-



Scheme 1. E: Y=H, F: Y=CHO or equivalent.

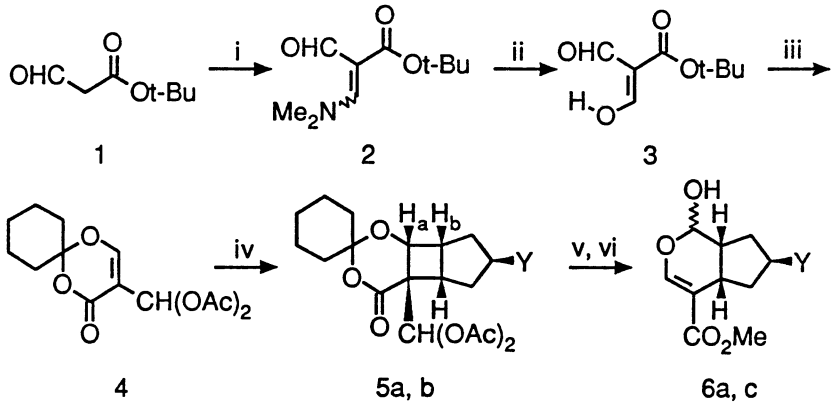
loganin[8] and (+)-sarracenin.[9] The method using chiral enophiles, however, suffers considerable practical drawbacks: 1) multistep sequences for the preparation of the chiral enophiles which had to be used in a large quantity, 2) poor regio- and enantioselectivities, and 3) inapplicability to the synthesis of an optically active **A** which necessarily requires achiral 3-cyclopenten-1-ol (**C**).

Previously, we have found that the photoaddition of chiral spirocyclic dioxinones (**E**) to cyclopentene proceeds not only with the a-side preference (a-side/b-side addition = ca. 6, by irradiation at room temperature) but also with an exclusive formation of the cis-anti-cis adduct.[10] The same a-side preference has also been observed in the 2-methyl derivatives of **E** by Demuth et al.[11] Clearly, if an enantiomerically pure spirocyclic dioxinone (**F**: Y=CHO or equivalent) which acts like diformylacetates (**B**) could be prepared conveniently and in preparative scale, the method would constitute a more efficient alternative to the enantioselective synthetic method of **A** and hence of optically active iridoids.

We report here some highly successful experiments both on the synthesis of chiral dioxinones (**F**) and their photoadditions to achiral cyclopentenes, by which **A** (a versatile synthon for iridoids) as well as its derivatives can become accessible conveniently in quantities and with very high optical purities.

In the preliminary study along this line, we first examined the synthesis of **4**. It is because in the photoaddition to cyclopentenes, the present methodology requires that, added to an obvious a-side preference,[10,11] the addition should also occur either by high endo/exo or by exo/endo preference.

The desired model compound (**4**, mp 100 °C)[12] was synthesized from tert-butyl formylacetate[13] **1** in ca. 60% overall yield by three steps shown in Scheme 2. The photoaddition of **4** to cyclopentene proceeded efficiently in ethyl acetate by irradiation at 300 nm (Rayonet photochemical reactor) and gave a single adduct (**5a**: mp 142 °C) in 75% isolated yield. The cis-syn-cis structure of **5a** is deduced by inspection of coupling constant (6.0 Hz) between Ha and Hb and was finally confirmed by X-ray crystallographic analysis (cf. Fig. 1).[14] Compared with an



a: Y=H, b: Y=OTBDMS, c: Y=OH

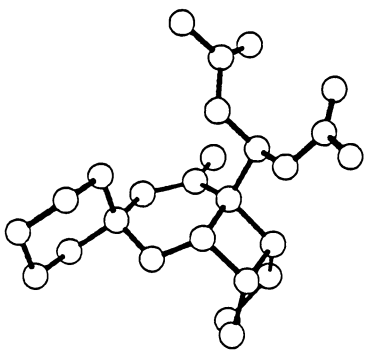


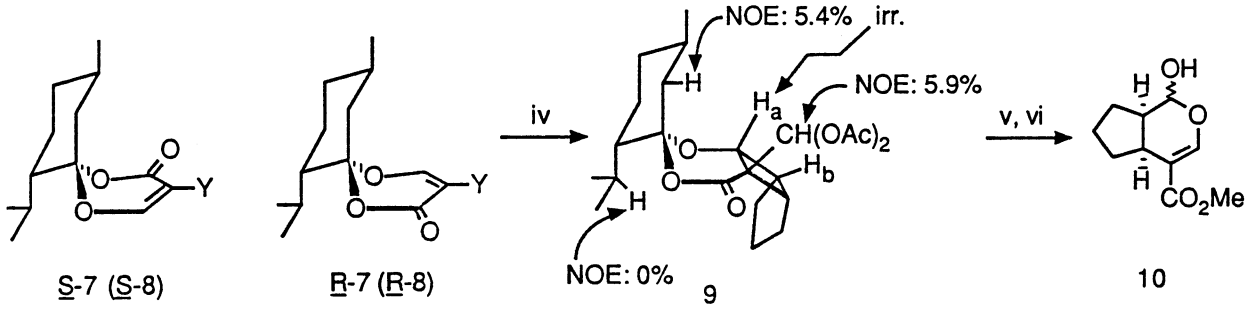
Fig. 1. Molecular structure of 5a.

Scheme 2. Reagents and conditions: i; $Me_2NCH(OMe)_2$, room temp , ii, 1 M NaOH, 0 °C, iii; cyclohexanone, conc. H_2SO_4, Ac_2O, 0 °C, iv; cyclopentene or 3-cyclopentene-1-ol TBDMS ether (10 equiv.), 300 nm, room temp , v; H_2O, room temp , p-TsOH (cat. amount), vi; CH_2N_2 / ether.

exclusive anti-addition as observed in the corresponding 2,3-unsubstituted dioxinones,[10,15] remarkable syn-preference of **4** in the photoaddition step seems to need comments. We assume that the bulkiness of diacetoxymethyl group of **4** prohibited the formation of the exo-adduct by steric reasons.

As shown in Scheme 2, the adduct was transformed to the deoxy bicyclic compound (**6a**) in 50% yield. When tert-butyldimethylsilyl (TBDMS) ether of 3-cyclopenten-1-ol was used as the enophile, two adducts (**5b**) were obtained in 57% yield in a ratio of ca. 9:1. Since cis-syn-cis structures were verified by NMR ($J_{Ha,Hb}$ = 6 Hz) for both adducts, it is evident that the adducts are stereoisomers concerning the silyloxyl group and the major adduct is **5b**-exo and the minor one is **5b**-endo.

Encouraged by the above model study, the corresponding chiral spirocyclic dioxinones (**S-7** and **R-7**) were synthesized from **3** and l-menthone by the same method shown in Scheme 2. Diastereomers of **7** (ca. 1:1 ratio from ^{1}H-NMR) were separated readily by fractional recrystallization from pentane to give the less (mp 109 °C, $[\alpha]_D$ -17.8°) and the more polar dioxinones (mp 97 °C, $[\alpha]_D$ -28.2°). Both compounds, when hydrogenated over palladium charcoal, gave the corresponding 3-methyl derivatives (S-**8** and R-**8**). Since the 6S-isomers of 2,3-unsubstituted dioxinones and their 2-methyl derivatives are always less polar than the 6R-isomers,[10,11,16] it is evident that the less polar dioxinones (S-**7** and S-**8**) have 6S-configuration and the more polar ones 6R-configuration (R-**7** and R-**8**).[17]



Scheme 3. Conditions and reagents: the same as those shown in Scheme 2.

Since the a-side preference in these dioxinones are obvious, the more polar dioxinone (R-**7**) was photoadded to cyclopentene. As a result, single adduct (**9**: oil) having cis-syn-cis structure ($J_{Ha,Hb}$ = 6.0 Hz) was obtained in 66% yield as the sole product. By NOE studies depicted in formula **9**, the structure was determined as being formed by the a-side addition. The adduct was transformed to **10** (oil, $[\alpha]_D$ -18.5°) in the same manner as in racemic series (**5**→**6** in Scheme 2).

We feel that the above results provide an alternative to Buchi's method for the synthesis of optically active iridoids[18] using chiral enophiles and should further help to increase the scope of applicability of spirocyclic dioxinones as chiral synthons for the synthesis of enantiomerically pure compounds.[19]

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14) Full details of the X-ray analysis will be published in the full paper.
15) 5,6-Unsubstituted dioxinones when photoadded to cyclopentene gave almost selectively the cis-anti-cis adducts, irrespective of the kind of substituent at 2-position: M. Sato, H. Ogasawara, K. Sekiguchi, and C. Kaneko, Heterocycles, 22, 2563 (1984). See also M. Sato, K. Sekiguchi, H. Ogasawara, and C. Kaneko, Synthesis, 1985, 224.
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