# Regioselective [2 + 2]-photocycloaddition reactions of chiral tetronates—influence of temperature, pressure, and reaction medium†‡

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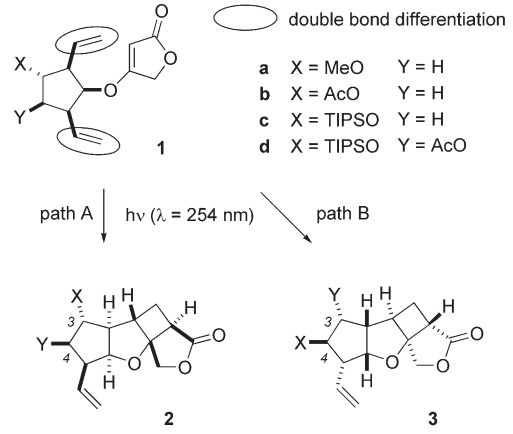
**The intramolecular [2 + 2]-photocycloaddition of the 1,3-divinyl-2-cyclopentyl tetronates 1 was performed under various conditions to give perfect diastereoselectivity and a regioselectivity of up to 85/15 in the presence of γ-cyclodextrin by differentiating the two chemically very similar double bonds of 1.**

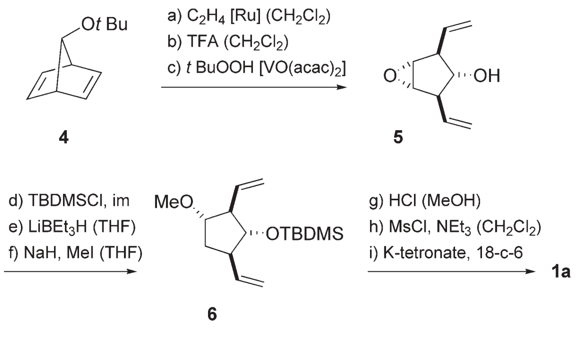
[2 + 2]-Photocycloaddition reactions belong to the most frequently employed photochemical transformations.[1] They allow for the construction of cyclobutanes,[2] the substitution pattern of which is governed by the photochemical substrate. The recently described tetronate photocycloaddition reactions provide a convenient, stereoselective access to 2-oxabicyclo[3.2.0]heptanes.[3] More specifically, the intramolecular photocycloaddition of a 1-vinyl-2-cyclopentyl tetronate leads in excellent diastereoselectivity to the 7-oxatricyclo [6.2.0.0$^{2,6}$] decane skeleton.[3b] Based on the occurrence of this structural motif in the sesquiterpene punctaporonine C[4] we have more closely investigated the photochemistry of substituted cyclopentyl tetronates. In the current study we addressed the regioselectivity issue in the [2 + 2]-photocycloaddition of substrates **1** (Scheme 1, TIPS = triisopropylsilyl). While the marked double bonds are diastereotopic if X = Y, they lead to regioisomeric products **2** and **3** if X ≠ Y. Hence, in this example, regio- and diastereotopos-selectivity[5] are closely related. From a synthetic point of view it is easier to address the positions C-3 and C-4 in the product for X ≠ Y, which was the reason why we chose the depicted substrates.

The synthesis of the photocycloaddition precursors started from the known[6] *tert*-butyl ether **4** and employed epoxide **5** as a common intermediate (Scheme 2). Ring opening metathesis[7] of diene **4** in the presence of ethylene was followed by acidic ether cleavage and a directed epoxidation.[8] Temporary protection of the secondary alcohol **5** was conducted with *tert*-butyldimethylsilyl chloride (TBDMSCl)–imidazole (im) in DMF. The epoxide ring opening was performed reductively for the synthesis of **1a–1c** or with HOAc for **1d** (see ESI†). The free secondary hydroxy group was subsequently converted into substituent X (*cf.* Scheme 1). Removal of the temporary protecting group, mesylation and nucleophilic displacement of the mesylate by a tetronate delivered the desired products **1**, as outlined for representative example **1a** in Scheme 2.



**Scheme 1** Selective intramolecular [2 + 2]-photocycloaddition to the vinylic double bonds of **1** leading to regioisomeric products **2** and **3**.

From previous work[3b] it is known that the intramolecular photocycloaddition of tetronates **1** occurs with the tetronate pseudoequatorially and the vinyl group pseudoaxially positioned. It was hoped that the substituents X and (for **1d**) Y would disturb the pseudoaxial positioning of one vinyl group so that it was not reactive any more. Initial photocycloaddition reactions were performed at ambient pressure and temperature (entries 1–4 in Table 1). It was shown that the reactions proceed cleanly and with



Specific conditions and yields: a) $RuCl_2(PCy_3)_2CHPh$ (4 mol-%), 25 °C, 7 d, 80%. b) 25 °C, 2 h. c) $VO(acac)_2$ (10 mol-%) in $CH_2Cl_2$, 0 °C to 25 °C, 6 h. d) DMF, 25 °C, 16 h, 43% (3 steps). e) 0 °C, 5 h, 93%. f) NaH, 0 °C, 1 h, then MeI, 25 °C, 6 h, 95%. g) 25 °C, 2 h, 90%. h) 0 °C, 4 h, 80%. i) DMF, 100 °C, 16 h, 40%.

**Scheme 2** Representative preparation of starting material **1a** from known[4] *tert*-butyl ether **4**.

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† Electronic supplementary information (ESI) available: Procedures for the preparation of **1a–1d**, **7**, NMR data of all intermediates and of the products **2**, **3**, **8**. See DOI: 10.1039/b613985j

‡ This paper is dedicated to Professor Rolf Gleiter (Heidelberg) on the occasion of his 70th birthday.

high diastereoselectivity. Only the two regioisomeric products **2** and **3** (Scheme 1), which are *cis–anti–cis* configurated, were observed. Diastereoisomers were not detected. Complete conversions translated into yields of isolated products in the range of 65–70% (see ESI†). Disappointingly, however, the regioisomeric ratios (r.r.) were close to unity for the four substrates. The best result was obtained with methyl ether **1a**, which delivered **2a** in a selectivity of 58/42. Interestingly, the direction of regioselectivity is not identical for the closely related substrates **1a–1c**. Apparently, the acetyloxy substituent favors formation of product **3b** (entry 2), while **2a** and **2c** prevail for methoxy and triisoproylsilyloxy substitution (entries 1, 3). The preference of triisopropylsilyloxy as X for **2** is reverted if an acetyloxy substituent is present as Y (entry 4). Variable temperature and pressure experiments revealed that neither $\Delta\Delta H^{\neq}$ nor $\Delta\Delta V^{\neq}$ are extremely large for the regioisomeric transition states. The most dramatic temperature effect was observed in the acetyloxy series. The temperature decrease led to a change in regioselectivity (entries 2 and 6). The fact that compound **3d** was favored significantly over **2d** at low temperature (entry 8) is preparatively interesting, because **3d** contains all stereogenic centers of punctaporonin C in the correct relative configuration. Unfortunately, the pressure influence on the reactions of substrate **1b** could not be studied due to decomposition under the irradiation conditions. In general, the reaction rate of the photocycloadditions decreased with increasing pressure (entries 9–11). This effect is readily explained by the fact that the conformation required for the photocycloaddition is not the most compact conformation.

The large influence of confined environments on the stereoselectivity of photochemical reactions is well documented. Conformations that are less populated in isotropic media under normal conditions can be favored in host–guest complexes.[9] Such observations prompted us to further investigate the influence of the reaction medium and confinement on the regioselectivity of our photocycloaddition reactions. We chose the well-studied cyclodextrins (CDs) for this purpose and conducted a set of experiments using β- and γ-cyclodextrins in MeOH–$H_2O$ or in $H_2O$ (Table 2).

**Table 1** Results obtained in the intramolecular photocycloaddition reaction of substrates **1** upon variation of temperature and pressure

| Entry | Substrate[a] | $T$/K | $p$/MPa | $t$/h | Conv.[b] (%) | r.r.[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | 298 | 0.1 | 1 | 100 | 58/42 |
| 2 | **1b** | 298 | 0.1 | 1 | 100 | 45/55 |
| 3 | **1c** | 298 | 0.1 | 1 | 100 | 56/44 |
| 4 | **1d** | 298 | 0.1 | 1 | 100 | 45/55 |
| 5 | **1a** | 213 | 0.1 | 2 | 100 | 59/41 |
| 6 | **1b** | 213 | 0.1 | 2 | 100 | 52/48 |
| 7 | **1c** | 213 | 0.1 | 2 | 100 | 54/46 |
| 8 | **1d** | 213 | 0.1 | 2 | 100 | 40/60 |
| 9[d] | **1a** | 298 | 0.1 | 3 | 62 | 58/42 |
| 10 | **1a** | 298 | 200 | 3 | 25 | 59/41 |
| 11 | **1a** | 298 | 400 | 3 | 20 | 60/40 |
| 12 | **1b** | 298 | 200 | 3 | — | — |
| 13 | **1c** | 298 | 200 | 3 | 25 | 56/44 |
| 14 | **1d** | 298 | 200 | 3 | 37 | 43/57 |

[a] All reactions were conducted at a substrate concentration of 1 mg $mL^{-1}$ (2.2–4.2 mM) in diethyl ether as the solvent. Irradiation source at 0.1 MPa: Rayonet RPR-2537 Å. Irradiation source at high pressure: Asahi Spectra LAX 101/102. [b] The conversion was determined by GLC analysis. [c] The regioisomeric ratio (r.r.) **2**/**3** was determined by GLC analysis. [d] The high pressure irradiation source was used.

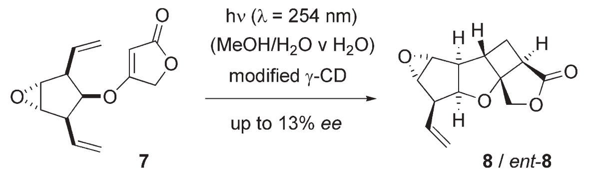
**Table 2** Results obtained in the intramolecular photocycloaddition reaction of substrates **1** upon variation of the reaction medium (CD = cyclodextrin)

| Entry | Substrate[a] | CD[b] | Solvent | $T$/K | Conv.[c] (%) | r.r.[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | β | MeOH–$H_2O$ | 298 | 100 | 65/35 |
| 2 | **1b** | β | MeOH–$H_2O$ | 298 | 100 | 56/44 |
| 3 | **1c** | β | MeOH–$H_2O$ | 298 | 85 | 56/44 |
| 4 | **1d** | β | MeOH–$H_2O$ | 298 | 90 | 53/47 |
| 5 | **1a** | β | $H_2O$ | 298 | 100 | 74/26 |
| 6 | **1b** | β | $H_2O$ | 298 | 100 | 45/55 |
| 7 | **1c** | β | $H_2O$ | 298 | 90 | 57/43 |
| 8 | **1d** | β | $H_2O$ | 298 | 67 | 82/18 |
| 9 | **1a** | γ | MeOH–$H_2O$ | 298 | 100 | 79/21 |
| 10 | **1b** | γ | MeOH–$H_2O$ | 298 | 100 | 60/40 |
| 11 | **1c** | γ | MeOH–$H_2O$ | 298 | 83 | 59/41 |
| 12 | **1d** | γ | MeOH–$H_2O$ | 298 | 26 | 65/35 |
| 13 | **1a** | γ | $H_2O$ | 298 | 100 | 83/17 |
| 14 | **1b** | γ | $H_2O$ | 298 | 100 | 47/53 |
| 15 | **1c** | γ | $H_2O$ | 298 | 83 | 55/45 |
| 16 | **1d** | γ | $H_2O$ | 298 | 69 | 82/18 |
| 17 | **1d** | γ | $H_2O$ | 313 | 100 | 85/15 |

[a] All reactions were conducted at a substrate concentration of 1.3 mM (entries 1–4), of 4.4 mM (entries 5–8), or of 3.8 mM (entries 9–17) at ambient pressure. Irradiation source: Eikosha 60 W low pressure Hg lamp. [b] 2.0 equivalents of the corresponding cyclodextrin were used. [c] The conversion was determined by GLC analysis. [d] The regioisomeric ratio (r.r.) **2**/**3** was determined by GLC analysis.

Again, the methyl ether **1a** was most susceptible to a change of conditions. It displayed a regioselectivity of up to 83/17 in favor of product **2a** (entry 13), when the reaction was conducted in an aqueous γ-CD solution. A dramatic effect was also observed for substrate **1d**, the double bonds of which were efficiently differentiated both in an aqueous β-CD (entry 8) and γ-CD solution (entry 16). The selectivity and conversion were further increased in the latter reaction **1d** → **2d**, if the temperature was increased to 313 K (entry 17). This reaction represents a [2 + 2]-photocycloaddition, in which the two pseudodiastereotopic vinylic double bonds were almost completely differentiated. After protecting group removal, X and Y are identical in **2d** and **3d** (X = Y = OH).

The pronounced influence of cyclodextrins on the double bond differentiation must be due to the previously mentioned conformation preferences in the appropriate host–guest complexes. Preparatively, it was tempting to see whether the cyclodextrins would also allow for an enantiotopos differentiation. The experiments were conducted with the symmetric divinylcyclopentyl tetronate **7** (Scheme 3) easily obtained from alcohol **5** by mesylation and nucleophilic displacement. Compared to the very good selectivity obtained for **2d** *vs.* **3d** the results were disappointing. Compared to several previous photochemical reactions enantioselectively mediated by CDs[9] the results are notable,



**Scheme 3** Differentiation of the enantiotopic double bonds of substrate **7** in its intramolecular photocycloaddition to **8** and *ent*-**8**.

however. An ee of up to 13% (±1% ee) was obtained with a modified acidic γ-cyclodextrin (see ESI†). The parent γ-cyclodextrin resulted in 5% ee. The absolute configuration of **8** and its enantiomer *ent*-**8** were not elucidated.

In summary, the regiocontrol mediated by γ-cyclodextrin was found to be effective for the intramolecular photocycloaddition of 1,3-divinyl-2-cyclopentyl tetronates **1a** and **1d**. A modified γ-cyclodextrin allowed for an enantiotopos-differentiation in substrate **7** (up to 13% ee). Further work is under way to study the conformational preferences of divinyl tetronates in cyclodextrins more closely.

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