



Application of chiral tethers to intramolecular [2+2] photocycloadditions: synthetic approach to (–)-italicene and (+)-isoitalicene

Sophie Faure^a and Olivier Piva^{b,*}

^aLaboratoire de Photochimie, UMR 6519 CNRS, Université de Reims Champagne-Ardenne UFR Sciences, BP 1039, F.51689 Reims cedex, France

^bLaboratoire de Chimie Organique, Photochimie et Synthèse, UMR 5622 CNRS, Université Claude Bernard-Lyon I, 43, Bd du 11 novembre 1918, F.69622 Villeurbanne, France

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Abstract—A synthetic approach to (–)-italicene and (+)-isoitalicene, sesquiterpenes which possess the rare tricyclo[5.4.0.0^{1,5}] undecane skeleton has been developed using as key step a highly regio- and diastereoselective [2+2] photocycloaddition. (*S*)-Lactic acid plays the role of a chiral removable tether group during the building of the cyclobutane ring. © 2000 Elsevier Science Ltd. All rights reserved.

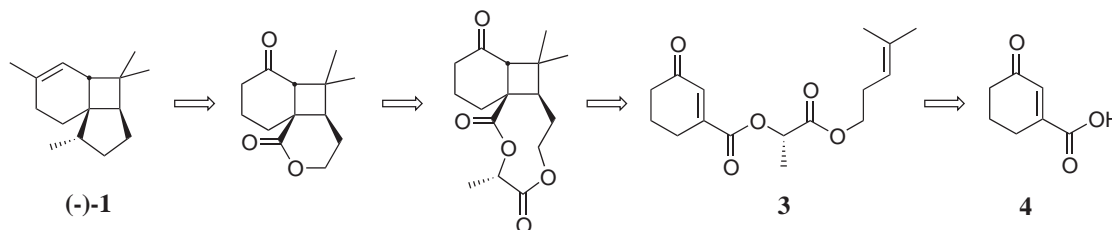
(–)-Italicene **1** and (+)-isoitalicene **2**, two sesquiterpenes isolated from the essential oil of *Helicrysum italicum*¹ are used nowadays as fragrance and natural insecticide in the mediterranean area. They possess both a cyclobutane framework which is relatively unusual in natural products (Scheme 1). To date, few approaches

or total syntheses have been reported and none was totally stereocontrolled.^{2–4}

While [2+2] cycloadditions^{5,6} can be considered as the most powerful way to prepare such 4-membered ring skeleta, we have investigated more particularly the asymmetric synthesis of these two compounds. Our approach was based on the use of α - or β -hydroxyacids as chiral tether for the intramolecular photocycloaddition process that we recently reported in a preliminary communication (Scheme 2).^{7a} Because the chiral auxiliary is connected both to the alkenone and the alkene moieties by two ester functionalities, this tether group can be removed in one single step to deliver the cyclobutane adduct in enantiomeric enriched form. The



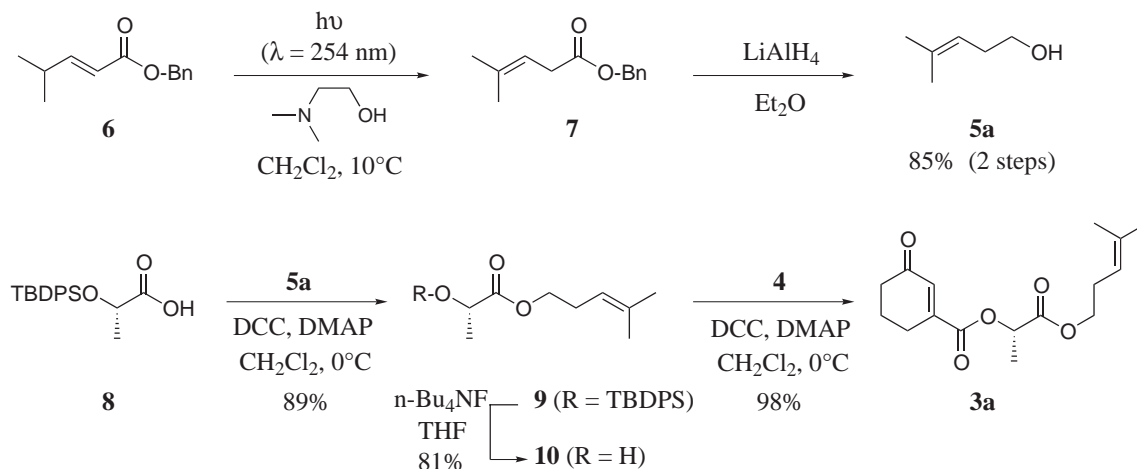
Scheme 1.



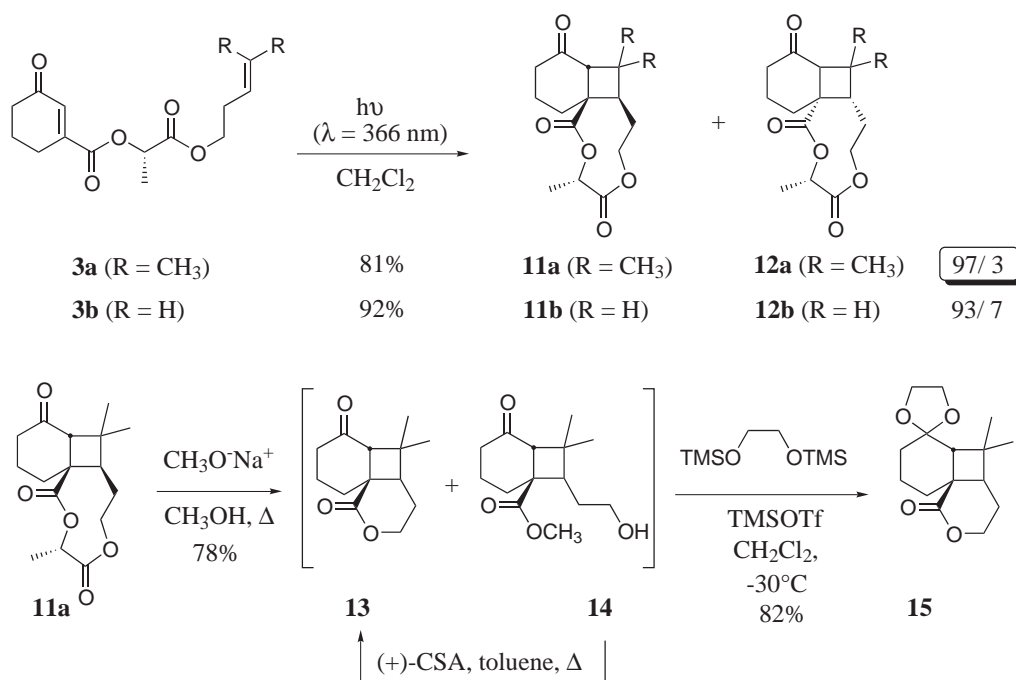
Scheme 2.

Keywords: italicene; cycloadditions; templates; metathesis; radicals.

* Corresponding author. Fax: +33-4-72-44-81-36; e-mail: piva@univ-lyon1.fr



Scheme 3.



Scheme 4.

easy cleavage is therefore one of the major advantage of this method, compared to other recent diastereoselective [2+2] photocycloadditions using different temporary chiral linkers.⁸

Starting oxoester **3a** was prepared from the known oxoacid **4**,⁹ protected (*S*)-lactic acid **8** and homoallylic alcohol **5a** (Schemes 2 and 3). This compound has been prepared by alternative routes but the more efficient combined the photodeconjugation¹⁰ and reduction of benzyl 4-methyl-2-pentenoate **6**.

Irradiation of **3a** (*R* = CH₃) was carried out in CH₂Cl₂ (10⁻² M) at rt and under a 366 nm wavelength and led to the formation of adduct **11a** in good yield and excellent regio- and diastereoselectivities. Only the formation of the straight compound was observed without

any trace of the other regioisomer, as already noticed with similar starting material **3b** (*R* = H).^{7b} The high level of induction (d.e. = 94%) was easily determined by ¹H NMR performed on the crude mixture before any purification step. This value appeared slightly better than the one observed for the unsubstituted butenyl derivative **11b** (*R* = H, d.e. = 86%). Moreover, the stereocourse of the reaction was attributed thanks to CD analyses on **11a** and **13** and comparison with previous results in this field.⁷ Removal of the chiral tether group was next performed by action of sodium methoxide, followed by treatment under slightly acidic conditions to favor lactonisation of the intermediate methyl hydroxyester **14** (Scheme 4).

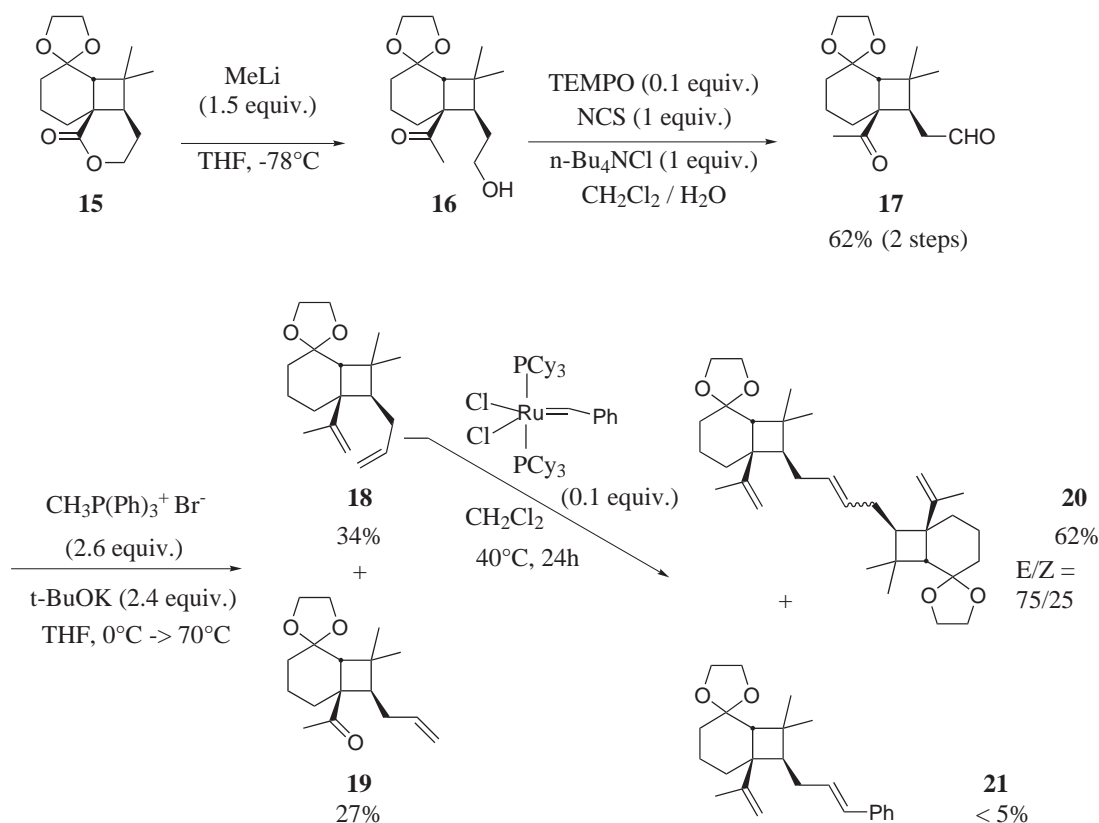
To reach the tricyclo[5.4.0.0^{1,5}] undecane skeleton, we investigated first a ring-closing metathesis (RCM) from

diene **18**.¹¹ This reaction has now emerged as a promising and powerful process for the synthesis of cycloalkenes since the discovery of efficient ruthenium¹² and molybdenum¹³ catalysts. Therefore, after protection of **13** under Noyori's conditions¹⁴ and action of MeLi in THF,¹⁵ hydroxymethylketone **16** was directly oxidised with TEMPO using Einhorn's conditions¹⁶ to ketoaldehyde **17**. Double Wittig reaction¹⁷ was conducted on **17** but, while the aldehyde reacted totally, the more hindered keto function was only partially converted into the methylene group. Using a large excess of reagents resulted only in degradation of the material. Fortunately, **18** and **19** were easily separated by flash-chromatography. Typical RCM conditions (10% Grubbs' catalyst, high dilution conditions) were applied to **18**. When performed at rt, no coupling occurred. By heating to 40°C, **18** was slowly converted into dimer **20** (*E/Z* = 75/25) resulting from a self-coupling process, while phenyl derivative **21** was also obtained as the only by-product (Scheme 5). The lack of reactivity of **18** for the intramolecular coupling could be attributed to the steric hindrance generated by the presence of a quaternary center α to one of the C=C bonds. Such limitations for the RCM has been widely reported, especially with the ruthenium catalyst used therein.^{11,18}

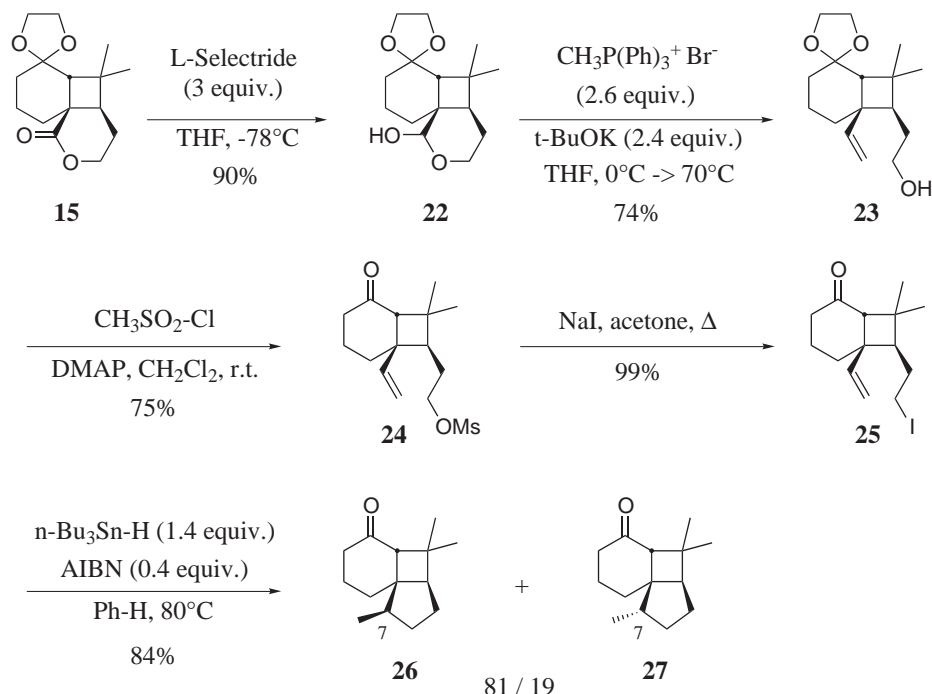
Since the RCM approach was not efficient, we chose a new strategy based on a radical cyclisation process¹⁹ of iodoalkene **25**. According to the Baldwin's rules,²⁰ a

5-*exotrig* process should take place and provide the expected tricyclo[5.4.0.0^{1,5}] undecane system. Lactone **15** was therefore reduced with L-selectride to lactol **22** in 90% yield. No further reduction occurred at this stage as already pointed out by Denmark et al.²¹ By a Wittig olefination using an excess of reagents, **22** was converted into unsaturated alcohol **23**, subsequently transformed into alkenyl iodide **25**.²² Standard radical cyclisation conditions applied to this substrate furnished two diastereomers **26** and **27** in good yield but moderate selectivity (81/19). The relative configuration of the new stereogenic center was assigned by comparison of its ¹H NMR spectrum and especially the chemical shift of CH₃ on carbon-7 with those of the natural products **1** and **2**, which possess the same stereodefined tricyclic core.²³ Therefore, the major diastereomer **26** appeared as a potential precursor of (+)-isoitalicene (Scheme 6).

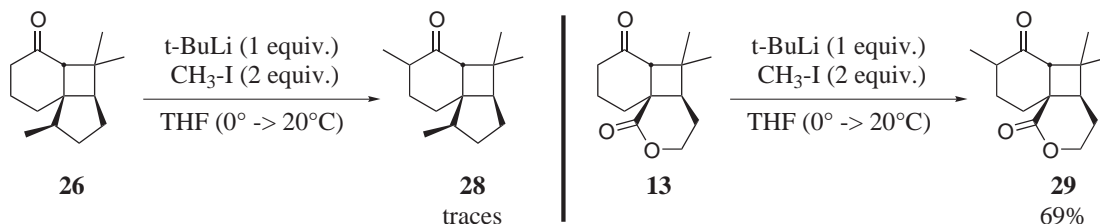
Attempts to introduce on **26** the methyl group in α -position of the carbonyl functionality appeared more difficult than expected, even by varying the nature of the base, solvent and additives. By contrast, starting from ketolactone **13**, methylation took place nicely (Scheme 7). Thus, introduction of the methyl substituent should be made before the radical sequence. Work is now underway to follow this strategy to complete the total and asymmetric synthesis of **1** and **2**.



Scheme 5.



Scheme 6.



Scheme 7.

Acknowledgements

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23. Characteristic shift for methyl group on carbon-7: **1**: $\delta = 0.77$ ppm (d, $J = 6.7$ Hz). **2**: $\delta = 0.82$ ppm (d, $J = 6.1$ Hz). **26**: $\delta = 0.89$ ppm (d, $J = 6.6$ Hz). **27**: $\delta = 0.82$ ppm (d, $J = 7.1$ Hz).