PHOTOADDITION WITH 1,2-BIS(TRIMETHYLSILOXY)CYCLOBUTENE: A VERSATILE ENTRY TO THE STEREOCONTROLLED TOTAL SYNTHESIS OF VARIOUS SESQUITERPENES AND DITERPENES†

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Summary

The photocycloaddition of 2-cyclohexenones to 1,2-bis(trimethylsiloxy)cyclobutene provides a short and versatile route to adequately functionalized decalins for the total synthesis of members of the following terpene classes: the eudesmanes, the eudesmanolides, the guaianes, the labdanes and the nagilactones. Regioselective and stereoselective manipulation of these key intermediates is discussed.

1. Introduction

Ring annulation reactions, whereby polycarbocyclic molecules are constructed, often constitute the central part of a synthetic scheme. In addition to the classical Robinson annulation and the Diels–Alder reaction, new methods are continuously being developed (for a review see ref. 1). Photochemical annulations often involve intramolecular ring closure of a suitable side-chain-containing parent compound. Usually, a number of reaction steps are needed to obtain the photoreactive molecule. Intermolecular ring construction by light relies in general on photocycloadditions of the type $[2\pi + 2\pi]$. It appears that such photocycloadditions take advantage of easy access to the reagents. We are particularly interested in the $[2\pi + 2\pi]$ photocycloaddition between conjugated cyclic enones and alkenes [2], in order to find *efficient* and *useful* prototypes. The term "efficient" covers such features as a high chemical yield, a good quantum yield, a clean reaction course and an easy work-up. The usefulness refers directly to the synthetic requirements: a smooth scaling-up to at least 1 mol, the clear option to introduce appropriate functional groups under complete regiocontrol and stereocontrol and

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a straightforward elaboration to more complex biologically active natural products. As such, the photoaddition serves as a principal step to yield versatile key intermediates.

2. Results and discussion

Since we are mainly concerned with the synthesis of polycarbocyclic terpenes, we utilize two simple cyclic reagents as starting materials: a conjugated cyclic enone, such as a substituted 2-cyclopenten one or 2-cyclohexenone, and a cyclic alkene, such as 1,2-bis(trimethylsiloxy)cyclopentene or 1,2-bis(trimethylsiloxy)cyclobutene (Fig. 1). The ketones can be purchased or can easily be prepared by standard methods. The alkene partner is synthesized in a one-pot reaction via internal acyloin condensation of the diester, whereby the intermediary dianion is trapped by trimethylsilyl chloride [3]. The photoreaction is performed as follows. The enone is selectively excited into the n,π^* region around 350 nm in an apolar solvent (*n*-hexane or *n*-pentane). The concentration of the enone amounts to 10^{-1} - 10^{-2} M or is even higher in preparations on a molar scale. In a typical experiment 1 or 2 equivalents of alkene are used, an excess being necessary for less-efficient reactions. After disappearance of the enone, the excess alkene is removed and the cycloadduct is distilled at a reduced pressure.

We have successfully applied the photoaddition between 2-cyclopentenones and 1,2-bis(trimethylsiloxy)cyclopentene in the total synthesis of a number of guaianolides and pseudoguaianolides [4]. These sesquiterpene classes contain a hydroazulenic or 7,5 ring system. The seven-membered ring is easily obtained by hydrolysis of the silyl ethers and subsequent oxidative 1,2-diol cleavage (Fig. 2). The pseudoguaianolides are constructed starting from 2-methyl-2-cyclopentenone via the stereospecific reduction of the carbonyl group in the cycloadduct and protection of the resulting alcohol as tetrahydropyranyl ether. Thus, the total synthesis of the ambrosanilides (a subgroup of the pseudoguaianolides) damsin [5], neoambrosin, parthenin and hymenin [6] has been developed in our laboratory. In addition carpesiolin [7] and hysterin [8], belonging to the subgroup of the helenanolides, have been synthesized.

This approach also led to the first reported total synthesis for the guaianolides compressanolide and estafiatin [9]. Here, the cycloadduct obtained from 2-cyclopentenone is subjected to a stereospecific organometallic treatment in order to obtain the key compound.

We now present an extension of the method, which has been proved to be even more versatile. Indeed, the photocoupling of 1,2-bis(trimethylsiloxy)-cyclobutene to cyclic enones is ideally suited to constructing hydrindanes or 6,5 ring skeletons and decalins or 6,6 ring systems, depending on the use of either 2-cyclopentenones or 2-cyclohexenones [10] (Fig. 3).

The essential feature in this approach is based on the fact that 1,2-bis-(trimethylsiloxy)cyclobutene serves as a latent cyclohexa-1,4-dione unit

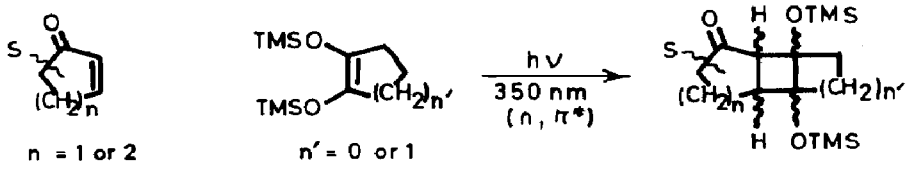

Fig. 1. General scheme for [2π + 2π] photocycloadditions (TMS, trimethylsilyl).

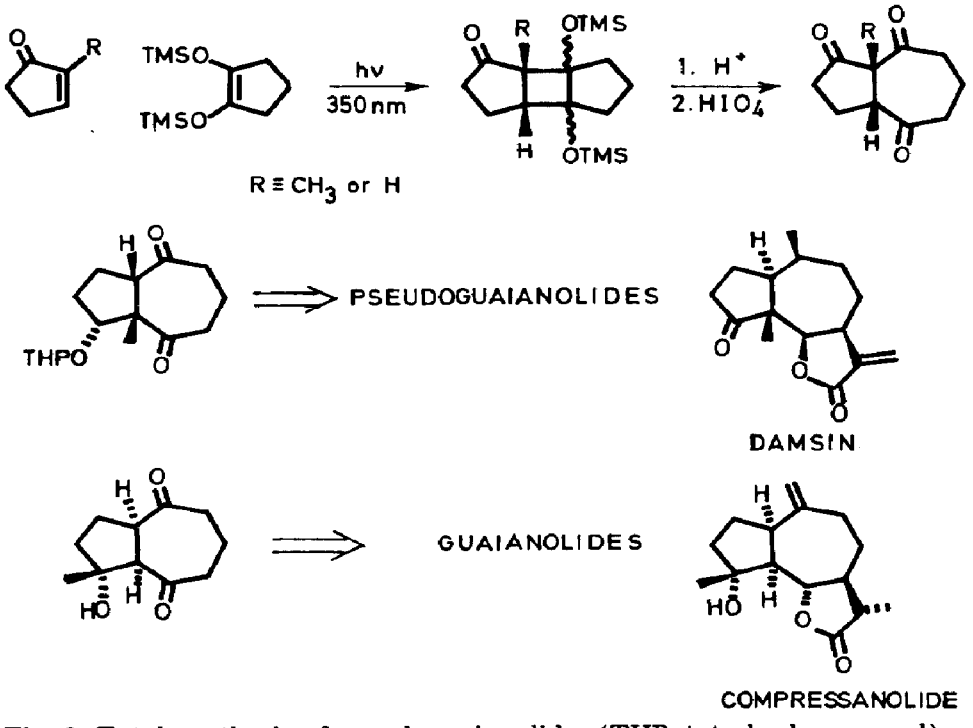

Fig. 2. Total synthesis of pseudoguaianolides (THP, tetrahydropyranyl).

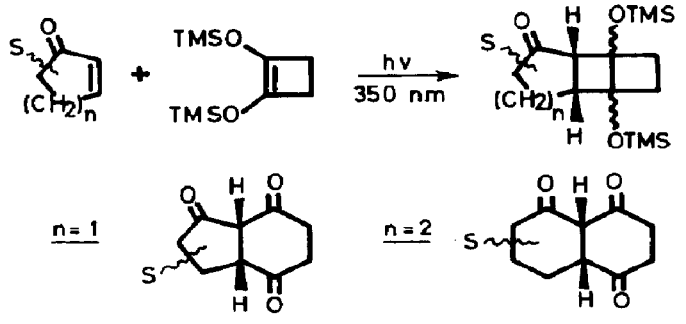

Fig. 3. Construction of 6,5 and 6,6 bicyclic systems.

obtainable on hydrolysis of the cycloadducts and oxidative cleavage of the resulting 1,2-diol. Until now we have not exploited the synthetic potential offered by the hydrindane ring assembly. Instead we have concentrated on the decalins since a wide variety of terpenes exist which possess this basic skeleton. Figure 4 displays some of our results in the 2-cyclohexenone series.

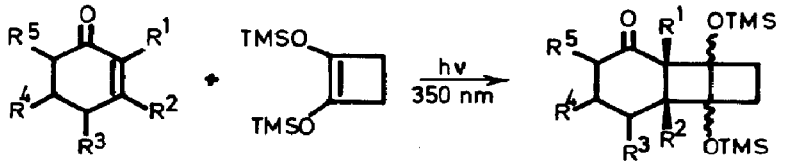

Fig. 4. Photocycloadditions of 2-cyclohexenones with 1,2-bis(trimethylsiloxy)cyclobutene.

Reaction	R^1	R^2	R^3	R^4	R^5	*Chemical yield* (%)
(1)	H	H	H	H	H	46
(2)	H	CH_3	H	H	H	77
(3)	H	CH_3	H	H	$CH(CH_3)_2$	85
(4)	H	CH_3	H	H	$CH_2CO_2CH_3$	60
(5)	H	CH_3	H	H	$CH(CH_3)CO_2CH_3$	60
(6)	H	CH_3	H	H	CO_2CH_3	68
(7)	CH_3	CN	H	H	H	96
(8)	CH_3	CH_3	CO_2CH_3	H	H	54

It should be noted first that further elaboration of a cycloadduct is not attempted if the chemical yield does not exceed 40%. Typical quantum yields for the examples shown are in the range 0.1 - 0.2. A number of other substituted 2-cyclohexenones were investigated, but the yield of photoadducts was low or complex reaction mixtures were produced or the compounds were photochemically unreactive. It has not yet been possible to present a rationale for the success or the failure of a given combination of reagents. Two factors are thought to be mainly responsible. First, the excited triplet states, which govern the photoannulation, are poorly defined because of the narrow energy gap between the respective n,π^* and π,π^* states; moreover, both can be reactive (new insights related to transient intermediates in the photochemistry of cyclohexenones have recently been reported [11]). Also the fate of the intermediary 1,4 diradicals depends very much on the substitution pattern. We have experienced that even small changes can completely divert the reaction pathway. For example, 3-cyano-2-methyl-2-cyclohexenone cycloadds to 1,2-bis(trimethylsiloxy)cyclobutene in 96% isolated yield (Fig. 4, reaction (7)), while both 2-methyl-2-cyclohexenone and 3-cyano-2-cyclohexenone lead to extremely complex mixtures under similar reaction conditions. In the following we shall highlight the utility of reactions (1), (3) and (5) (Fig. 4) in the total synthesis of various sesquiterpenes and diterpenes.

Since four new chiral centres are produced in the photoaddition, interesting stereochemical features are involved. Whilst photocycloaddition of simple electron-rich alkenes to 2-cyclohexenones gives rise to both *cis*-coupled and *trans*-coupled adducts [12], the amount of *trans*-annulated products was less than 1% in the systems we studied. Furthermore, we nearly exclusively isolate *cis-anti-cis* structures, as displayed in Fig. 5. Only in reaction (1) (Fig. 4) was the amount of *cis-syn-cis* compound 10%. We have formerly developed a simple mass spectrometry method to distinguish between

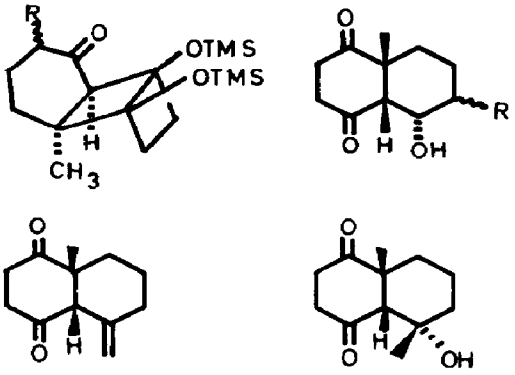

Fig. 5. Key photoproducts for the synthesis of terpenes.

R	*Yield (%) of α-R*	*Yield (%) of β-R*
$CH_2CO_2CH_3$	30	70
$CH(CH_3)CO_2CH_3$	10	90
$CH(CH_3)_2$	< 10	> 90

these stereoisomers [13]. However, since this stereochemical differentiation disappears on subsequent ring cleavage, both isomers are suitable for further work. As a result of the facile retro-aldol reaction after hydrolysis of the silyl ethers, the carbonyl group must be transformed first in the cycloadduct. Thus sodium borohydride reduction yields the *endo* alcohol exclusively as a result of hydride attack from the least-hindered *exo* face. Acid hydrolysis and periodate cleavage of the 1,2-diol lead to the key bicyclic hydroxy diketone (Fig. 5).

Again, the stereochemistry is intriguing. The key compound has a *cis* junction as imposed in the photoaddition reaction. Facile epimerization is induced by acid or base treatment. The equilibrium ratio is typically 9:1 in favour of the more stable *trans* compound. Nearly quantitative transformation is achieved by recycling of the mother liquor after crystallization of the *trans* decalins. It should be noted that, in the terpenes that we want to synthesize, *trans* annulation always prevails. Still more important is the stereochemistry of the alkyl group (Fig. 5, R). As shown in Fig. 5, the β configuration predominates in the resulting decalins. This reflects the high stereoselectivity of the photocycloaddition, which is in accordance with Wiesner's rule [14]. As can be seen, the selectivity is more pronounced the more space demanding the substituent R is. This feature is of vital importance since only the isomer carrying the R substituent in the *cis* position with respect to the angular methyl group is suitable for the syntheses that we want to pursue. The above-cited configurational control has frequently been problematic in previous synthetic work on eudesmanes [1, 15]. Also displayed in Fig. 5 are two related bicyclic diketones which have been prepared via Wittig and organometallic reactions on the photoadduct. These bicyclic

compounds (Fig. 5) are then the key building blocks, which either contain the stereochemical features necessary for further elaboration or have the provisions for the stereoselective introduction of suitable functional groups. The overall yield from the two monocyclic starting reagents varies between 40% and 60%, *i.e.* about 80% on average for each of the four reaction steps. This is also valid for preparations on a molar scale.

3. Applications

It is not possible to treat in detail each individual total synthesis that we have carried out. Our purpose is rather to demonstrate the versatility of the photochemical approach. Thus, we obtained smooth access to 1-oxygenated eudesmane sesquiterpenes, such as dihydrodictyopterone [16] and 1-oxocostic acid [17] (Fig. 6). These representatives only differ in the nature of the side-chain. Key elements are the elimination of the hydroxyl function and the regioselective Wittig reaction. The total synthesis of dihydroreynosin [18] (Fig. 6) is particularly interesting. The exact configuration of the four chiral centres on the ring carbon atoms in the key bicyclic compound is provided for in the photoaddition step itself or in a subsequent reaction. It is found that the introduction of the two extra chiralities is completely stereocontrolled by the functional groups present. Indeed, we isolated a stereohomogeneous trimethylsilyl ether (95% yield) with the side-chain methyl group in the α position [18]. Thus, complete epimerization has occurred under the reaction conditions. Further, this trimethylsilyl ether efficiently blocks the adjacent carbonyl group, whereby the remaining carbonyl function can be reduced, again in a stereospecific fashion. Afterwards, the extra carbon atom is introduced by a Wittig reaction and the lactone ring can consequently be formed. As a result, dihydroreynosin is obtained under total stereocontrol. This compound in fact belongs to the subclass of eudesmanolides, which features a γ lactone function.

A closely related series of eudesmanolides consists of magnolialide, dihydromagnolialide, 1-oxodihydromagnolialide and maritimin (Fig. 7) [18]. The extra methyl group is stereoselectively introduced with methyllithium. Maritimin is the α epoxide of 1-oxodihydromagnolialide which occurs for 80% of the diastereomeric mixture after *m*-chloroperbenzoic acid treatment. In the synthesis of 1-epidihydromagnolialide the non-stereoselective reduction of the key compound with potassium tri-*sec*-butylborohydride is applied. The α alcohol, which slightly predominates in the mixture (ratio, 5:4), is isolated by column chromatography. To obtain dihydrosantamarin, a regioisomer of dihydromagnolialide, a *syn* elimination is involved following the methyllithium reaction. Formation of the *endo* double bond is favoured by a factor of 4:1 over the *exo* isomer. It is obvious that the present method is also very well suited to synthesizing α-santonin (Fig. 7), the eudesmanolide with which photochemists are certainly most familiar [19]. The key transformation is allylic oxidation of the dihydromagnolialide skeleton, followed by a straight-

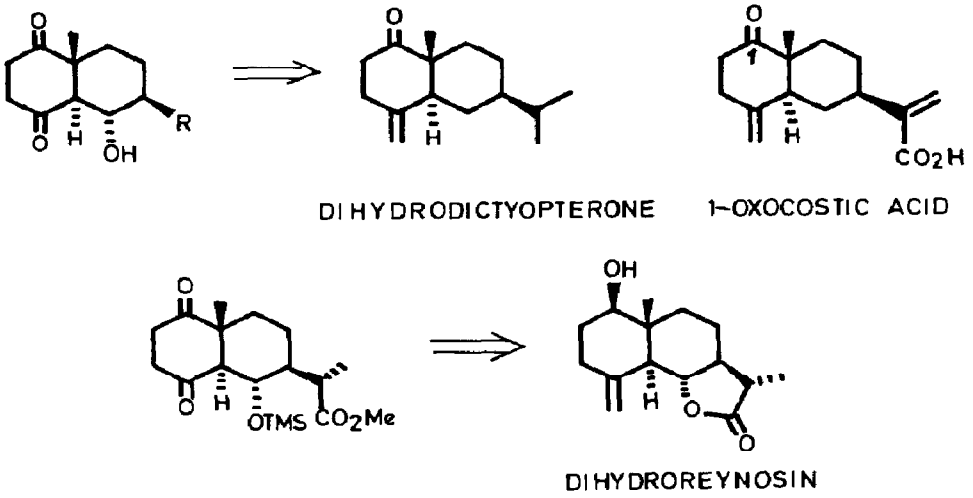

Fig. 6. Total synthesis of eudesmanes.

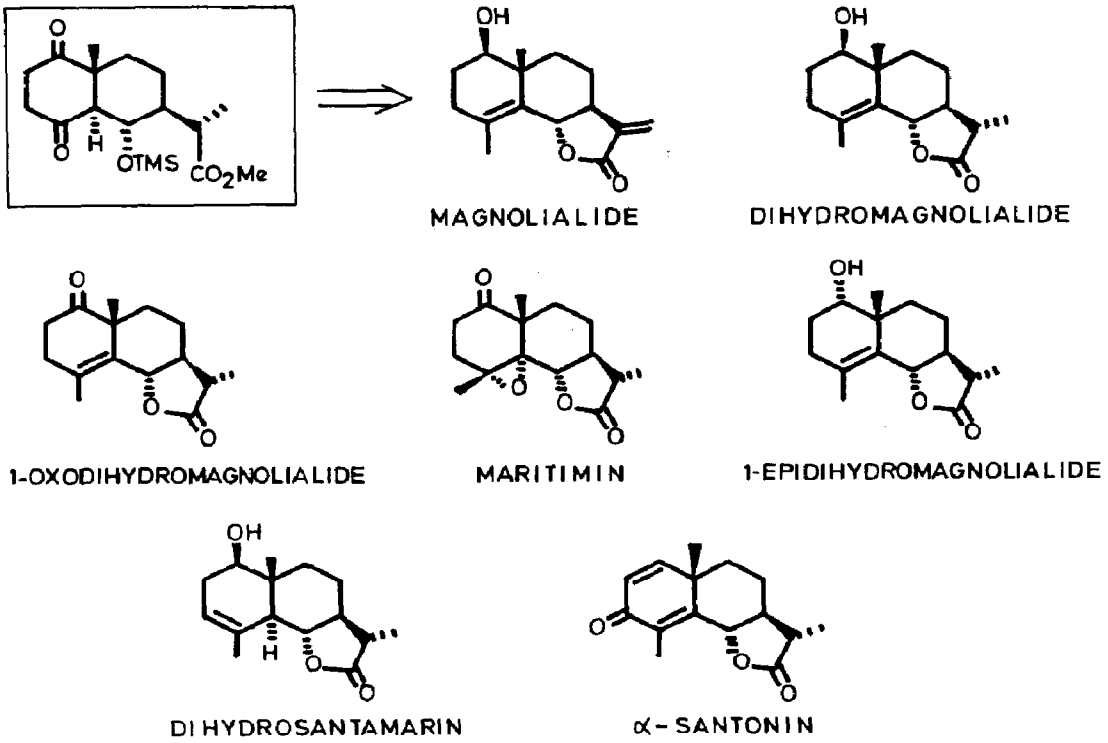

Fig. 7. Total synthesis of eudesmanolides.

forward elimination reaction [18]. Entry to the perhydroazulenic or 7,5 ring system is a further opportunity offered by the current approach. The key bicyclic compound is transformed in several reaction steps to the important 1-tosyloxyeudesmane derivative, which is then solvolysed in a Heathcock-type rearrangement to a 7,5 bicyclic system [20]. Modification of the side-

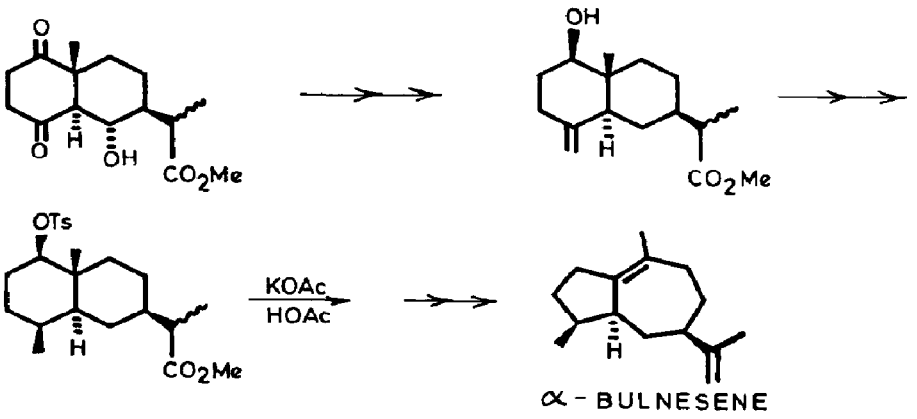

Fig. 8. Total synthesis of guaianes (OTs, tosyl).

chain yields α-bulnesene (Fig. 8), a member of the so-called guaiane sesquiterpenes.

A recent development of our method intends to open a new, short and efficient route to polycyclic diterpenes [21]. Until now, we have probed into two classes: the labdanes, such as marrubiin and the labdane-derived mould metabolite LL-Z1271α, and the nagilactones, such as nagilactone F (Fig. 9).

In particular these norditerpenoid dilactones are interesting target molecules showing biological activity. The synthetic plan centres around the key tricyclic lactone, represented in Fig. 9. We have prepared this lactone in eight reaction steps with an overall yield of 18% including the photocycloaddition. Since this intermediate has already been used by Welch *et al.* [22] and Mangoni *et al.* [23] in the total synthesis of marrubiin and of LL-Z1271α, our approach constitutes a formal alternative synthesis of these compounds. Furthermore, Hayashi *et al.* [24] have performed a relay synthesis of nagilactone F in 17 reaction steps from the natural podocarpic acid. Possibly our tricyclic ketone could serve as an intermediate for an efficient total synthesis of nagilactone F.

4. Conclusion

We have described a prototype for an efficient and useful [2π + 2π] photoreaction: the cycloaddition of 1,2-bis(trimethylsiloxy)cyclobutene to substituted 2-cyclohexenones. Versatile key intermediates are obtained, even on a molar scale, in a few straightforward reaction steps. The approach allows for complete stereocontrol in the further elaboration to more complex biologically active terpenes. As such, short and effective synthetic schemes are designed, which completely rely on the photochemical contribu-

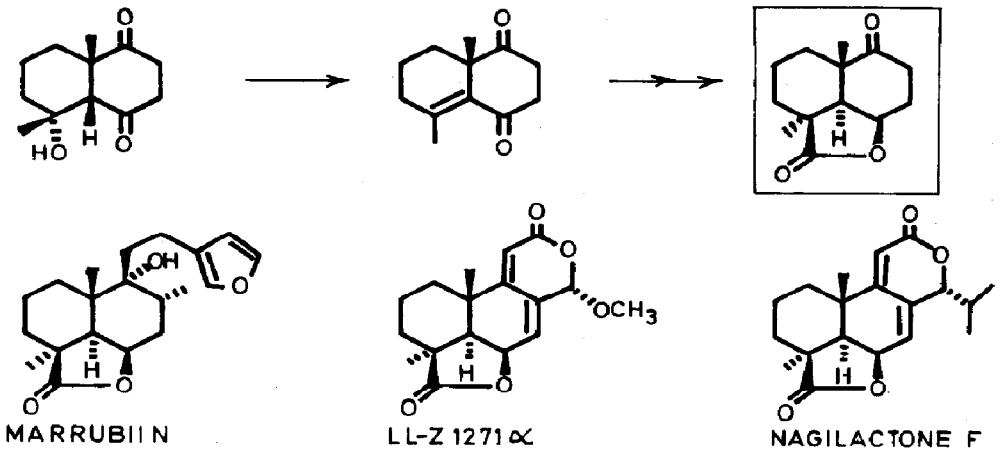

Fig. 9. Total synthesis of diterpenes.

tion. Indeed, photochemistry can and should play a vital role in contemporary synthetic chemistry.

Acknowledgments

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References

1 M. Vandewalle and P. De Clercq, *Tetrahedron, 41* (1985).
2 D. Termont, D. De Keukeleire and M. Vandewalle, *J. Chem. Soc., Perkin Trans. I,* (1977) 2349.
3 J. J. Bloomfield, *Tetrahedron Lett.*, (1968) 587.
K. Rühlmann, *Synthesis*, (1971) 236.
4 D. Termont, P. De Clercq, D. De Keukeleire and M. Vandewalle, *Synthesis*, (1977) 46.
5 P. De Clercq and M. Vandewalle, *J. Org. Chem., 42* (1977) 3447.
6 M. Vandewalle, P. De Clercq, M. Demuynck, P. Kok, G. Rozing and F. Scott, in W. Bartmann and E. Winterfeldt (eds.), *Proc. Hoechst Workshop Conf., Schloss Reisenburg, September 24 - 27, 1978*, in *Excerpta Med.*, (1978) 130.
7 P. Kok, P. De Clercq and M. Vandewalle, *J. Org. Chem., 44* (1979) 4553.
8 M. Demuynck, P. De Clercq and M. Vandewalle, *J. Org. Chem., 44* (1979) 4863.
9 A. Devreese, M. Demuynck, P. De Clercq and M. Vandewalle, *Tetrahedron, 39* (1983) 3039, 3049.
10 M. Van Audenhove, D. De Keukeleire and M. Vandewalle, *Tetrahedron Lett., 21* (1980) 1979.

11 D. I. Schuster, R. Bonneau, D. A. Dunn, J. M. Rao and J. Joussot-Dubien, *J. Am. Chem. Soc., 106* (1984) 2706.
12 E. J. Corey, J. D. Bass, R. Le Mahieu and R. B. Mitra, *J. Am. Chem. Soc., 87* (1964) 5570.
13 M. Van Audenhove, D. De Keukeleire and M. Vandewalle, *Bull. Soc. Chim. Belg., 89* (1980) 371.
14 G. Marini-Bettolo, S. P. Sahoo, G. A. Poulton, T. Y. R. Tsai and K. Wiesner, *Tetrahedron, 36* (1980) 719.
15 C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac and C. T. White, in J. ApSimon (ed.), *The Total Synthesis of Natural Products*, Vol. 5, Wiley, New York, 1983, p. 124.
16 M. Van Audenhove, D. De Keukeleire and M. Vandewalle, *Bull. Soc. Chim. Belg., 90* (1981) 255.
17 L. Van Hijfte and M. Vandewalle, *Tetrahedron Lett., 23* (1982) 2229.
18 L. Van Hijfte and M. Vandewalle, *Tetrahedron, 40* (1984) 4371.
19 D. H. R. Barton, P. de Mayo and M. Shafiq, *J. Chem. Soc.*, (1958) 140.
20 C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc., 93* (1971) 1746.
21 L. Van Hijfte and M. Vandewalle, *Synth. Commun., 14* (1984) 1149.
22 S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming and J. W. Trotter, *J. Am. Chem. Soc., 99* (1977) 549.
23 L. Mangoni, M. Adinolfi, G. Laonigro and R. Caputo, *Tetrahedron, 28* (1972) 611.
24 Y. Hayashi, T. Matsumoto, T. Hyono, N. Nishikawa, M. Vemura, M. Nishizawa, M. Togami and T. Sakan, *Tetrahedron Lett.*, (1979) 3311.