Available online at www.sciencedirect.com
SCIENCE DIRECT®
C. R. Chimie 6 (2003) 547–552
COMPTES RENDUS CHIMIE

Account / Revue

Stereo- and enantioselective reactions. Application to the synthesis of biologically active compounds

Janine Cossy *, Samir BouzBouz, Matthew Popkin

Laboratoire de chimie organique, associé au CNRS, ESPCI, 10, rue Vauquelin, 75231 Paris cedex 05, France

Received 23 December 2002; accepted 11 April 2003

Abstract

Enantioselective allyltitanation as reactions as well as ring closing metathesis reaction have been used to synthesize biologically active compounds. ***To cite this article: J. Cossy et al., C. R. Chimie 6 (2003).***

Résumé

Des allyltitanations énantiosélectives et de fermeture de cycle par métathèse ont été mises au point pour synthétiser des produits biologiquement actifs. ***Pour citer cet article : J. Cossy et al., C. R. Chimie 6 (2003).***

Keywords: allyltitanation; enantioselectivity; metathesis; passifloricin A; staurosporine; discodermolide

Mots clés : allylation ; énantiosélectivité ; métathèse ; passifloricine A ; staurosporine ; discodermolide

One of the major challenges in synthetic organic chemistry is the design and execution of concise approaches and strategies to complex molecules by using reactions that rapidly lead to their carbon skeleton. In this context, we have explored the construction of molecules having diol and polypropionate units by tuning up regio-, chemo-, stereo- and enantioselective reactions.

Asymmetric C–C bond formation is an attractive synthetic strategy, as the connectivity of a carbon framework and its configuration are established simultaneously. The allylmetallation of aldehydes and ketones, leading to products with a maximum of two new stereocentres and versatile functionalities for further transformations is an important method for acyclic stereocontrol [1–5]. Efficient chirality transfer from allyl moieties has been obtained with chiral allylmetal reagents [6–13]. In the 1980s, organotitanium reagents opened new perspectives for high selectivity, as their structural variability allows the necessary adjustments for reactivity [14–19]. Duthaler and Hafner prepared a variety of such chiral organotitanium reagents and among them, chiral cyclopentadienyldialkoxytitanium (IV) complexes [20, 21]. They screened them for enantioselective allyltitanations and crotyltitanations and

* Corresponding author.
E-mail address: janine.cossy@espci.fr (J. Cossy).

doi:10.1016/S1631-0748(03)00082-1

they discovered that the presence of the (*R,R*)-tartrate ligand in complex (*R,R*)-**I** and (*R,R*)-**II** allows the transfer of allyl and crotyl groups to aldehydes with high *si* face selectivity and that the presence of the (*S,S*)-tartrate ligand in complex (*S,S*)-**I** and (*S,S*)-**II** allows the transfer of allyl and crotyl groups to aldehydes with high *re* face selectivity [22, 23]. A wide range of homoallylic alcohols with high enantiomeric excess was obtained by using these complexes (Fig. 1).

Nevertheless, it was desired to develop methodologies for the stereocontrolled obtention of 1,2- or 1,3-diol units as well as polypropionate units to prepare biologically active compounds such as LY 33 35 31, passifloricin A and discodermolide (Fig. 2).

The first product that we became interested in was LY 33 35 31 related to the naturally occurring staurosporine, which is a Protein Kinase C inhibitor. This

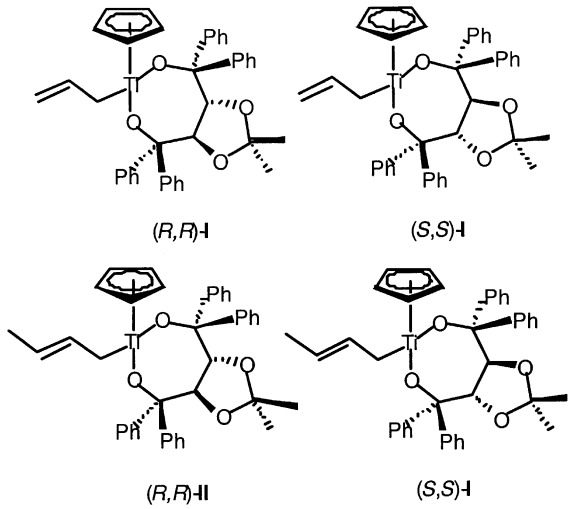

Fig. 1. Enantioselective allyl- and crotyltitanium complexes.

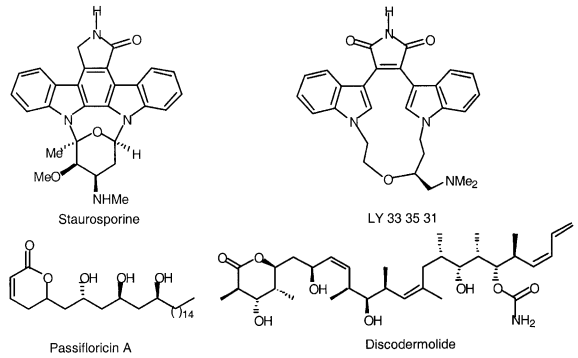

Fig. 2. Biologically active compounds.

compound was obtained by others with alkylation of **1** with bis-mesylate **2**, which was synthesized from the expensive (*R*)-1-chloro-2,3-propanediol **3** with an overall yield of 45–55% and an enantiomeric excess of 98% [24–26] (Fig. 3).

By using an enantioselective allyltitanation, we were able to transform the cheap allylic alcohol **4** to the bis-mesylate **2** in six steps, in good yield (66%) and with good enantiomeric excess (98%) (Fig. 4) [27].

If 1,2-diols are found in a great number of biologically active compounds, the 1,3-diol functionality is of great importance for the biological activity of many pharmaceutical products. Therefore, it is not surprising that numerous strategies have been developed for the stereoselective synthesis of compounds containing 1,3-diol units [28–30].

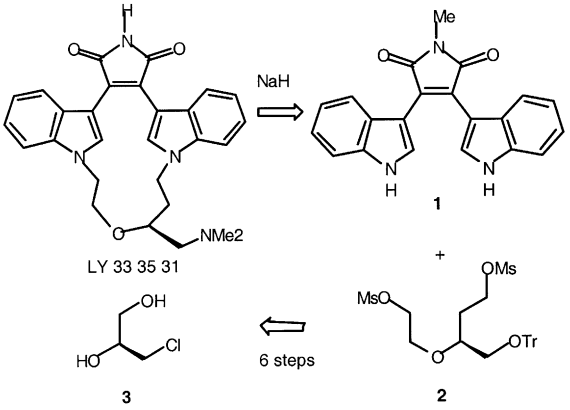

Fig. 3. Retrosynthetic analysis of staurosporine.

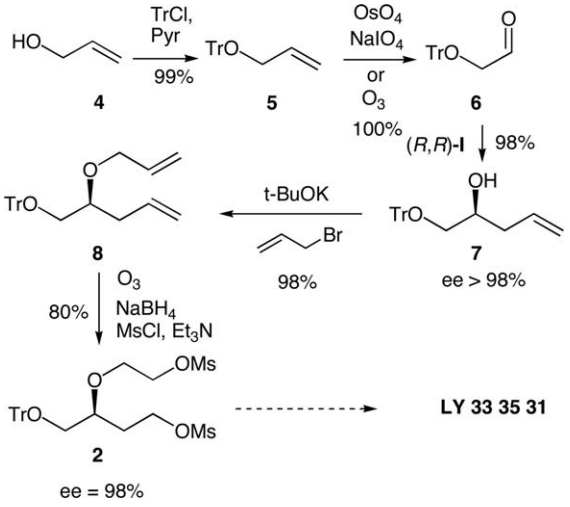

Fig. 4. Synthesis of the precursor of LY 33 35 31.

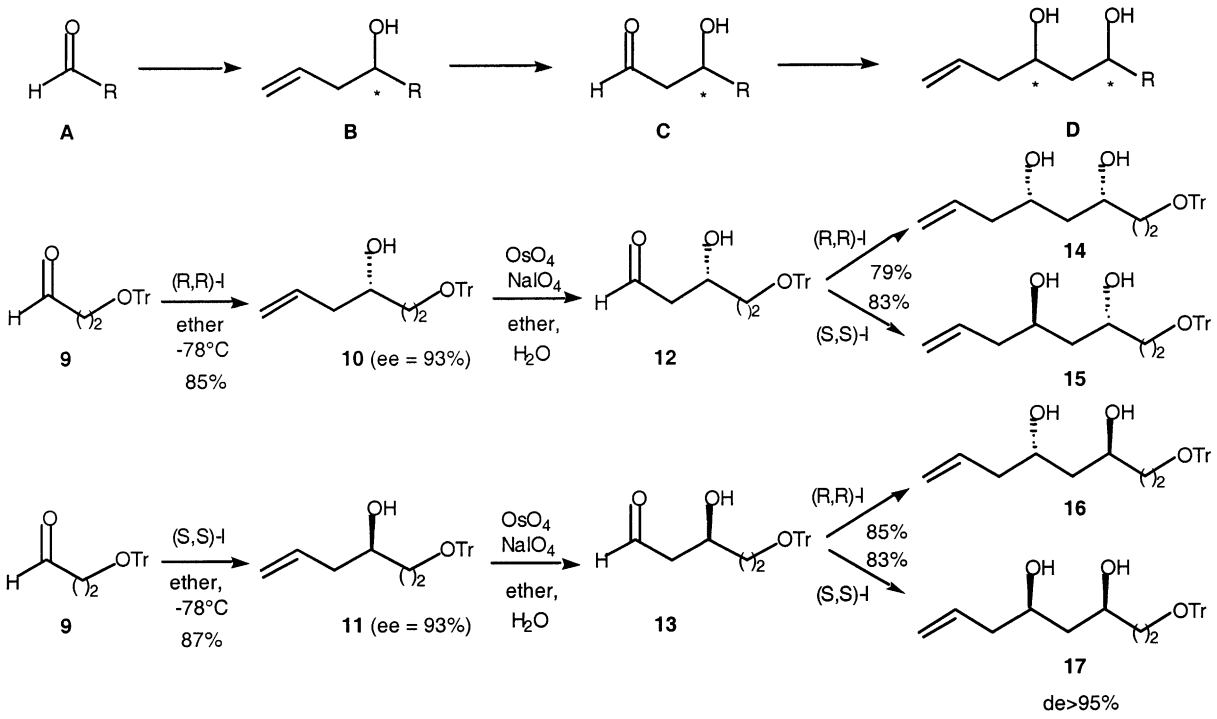

Fig. 5. Synthesis of 1,3-diols *syn* and *anti*.

We have synthesized *syn*- as well as *anti*-1,3 diols of type **D** from aldehyde of type **A** with good to excellent enantiomeric excess by using the allyltitanium complexes (*R*,*R*)-**I** and (*S*,*S*)-**I** (Fig. 5). For example, 1,3-diols **14–17** were obtained in good yield (67–72%) and good enantiomeric excess (93%) from aldehyde **9** [31]. After the allyltitanation of aldehyde **9** by using (*R*,*R*)-**I** or (*S*,*S*)-**I**, the obtained homoallylic alcohols **10** and **11** were oxidatively cleaved (OsO_4/NMO; $NaIO_4$) and the unstable β-hydroxy aldehydes **12** and **13** were treated directly with the allyltitanium complexes. When the non-protected β-hydroxy aldehydes **12** and **13** were treated respectively with (*R*,*R*)-**I** and (*S*,*S*)-**I**, the *syn*-1,3-diols **14** and **17** were respectively obtained in high yield (79–85%) and with a diastereomeric excess superior to 95%. When β-hydroxy aldehydes **12** and **13** were treated respectively with (*S*,*S*)-**I** and (*R*,*R*)-**I**, the *anti*-1,3-diols **15** and **16** were isolated in high yield (79–83%) and with a diastereomeric excess superior to 95%. The formation of *syn*- or *anti*-1,3-diols from non-protected β-hydroxy aldehydes of type **C** by using (*R*,*R*)-**I** or (*S*,*S*)-**I** is very general. The most important feature in these allyltitanations is that 1,3-diols can be obtained without any protective or deprotective steps, which enhances the synthetic potential of this organometallic allylation reaction (Fig. 5). We have also demonstrated that acid-sensitive (silyl ether, trityl ether) or base-sensitive (benzoyl) protecting groups can be tolerated in these allyltitanations [31].

Non-protected 1,3-diols are interesting intermediates, which offer an efficient entry to the synthesis of natural products such as passifloricin A, an antifungal agent recently isolated, for which the absolute configuration of the stereogenic centres has to be confirmed by synthesis, as two different structures **E** and **F** have been reported in the literature (Fig. 6) [32].

We chose to synthesize structure **E**. The synthesis of **E** has been achieved from hexadecanal **18**. As the reagents (*R*,*R*)-**I** and (*S*,*S*)-**I** are highly face-selective, the stereogenic centres were controlled by adding (*R*,*R*)-**I** and (*S*,*S*)-**I** to the corresponding aldehydes

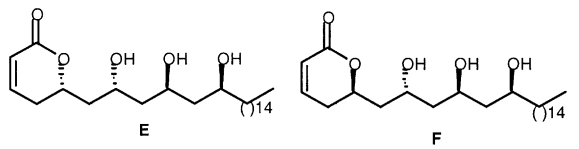

Fig. 6. Possible structures for passifloricin A.

(Fig. 7). Compound **19** was obtained by this process and transformed into compound **E** in a three-step sequence. Unfortunately, the spectroscopic data do not correspond to those of passifloricin A. This leads to suspect that passifloricin A has structure **F** (Fig. 7).

The polypropionates (chains with alternating methyl-hydroxy-methyl substituents) [33] represent an important class of natural products such as the ionophores, the lactones and the macrolides [34–37]. Associated with a broad spectrum of biological activity, these structures encompass a large diversity of molecular architecture.

In looking for routes to prepare (+)-discodermolide, our interest was drawn to build up stereotetrads and stereopentads as these units are present in this compound. We have synthesized stereotetrads from *meso*-dialdehydes with good dia- and enantioselectivities. For example, when *meso*-dialdehyde **21** was treated with (*R*,*R*)-**I**, lactol **22** was obtained and reduced with $NaBH_4$ to furnish compound **23** in 49% overall yield [38] (Fig. 8). It is worth noting that (*R*,*R*)-**I** discriminates the pro(*S*) face of the aldehyde. Furthermore, the

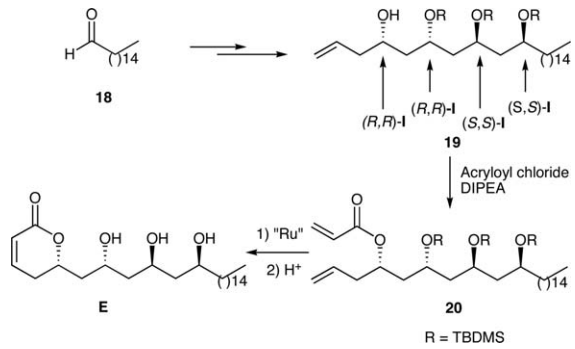

Fig. 7. Synthesis of an analogue of passifloricin A.

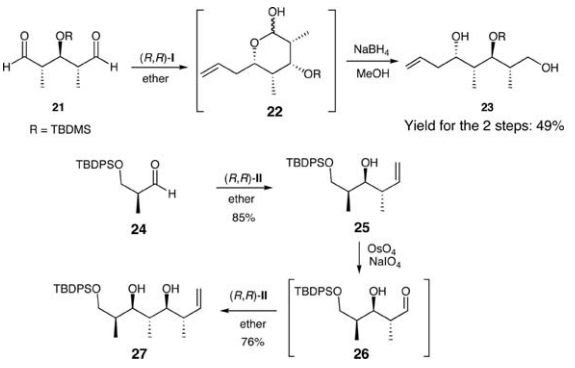

Fig. 8. Synthesis of stereotetrads.

allyltitanations have been shown to closely follow a Felkin–Anh transition state [38].

The stereotetrads have also been synthesized from aldehyde of type **A** with good to excellent diastereoselectivity and enantioselectivity by using the crotyltitanium complexes (*R*,*R*)-**II** and (*S*,*S*)-**II**. For example, stereotetrads **26** have been obtained from aldehyde **24** by using two crotyltitanations [39]. After treatment of aldehyde **24** with (*R*,*R*)-**II**, the obtained homoallylic alcohol **25** was oxidatively cleaved (OsO_4/NMO, $NaIO_4$) and the β-hydroxyaldehyde **26** was treated directly with the crotyltitanium complexes. When **26** was treated with (*R*,*R*)-**II**, the stereotetrads **26** and **27** were respectively obtained in high diastereoselectivity (> 95%) and enantioselectivity (Fig. 8) [39]. As in the case of the allyltitanium complexes, the crotyltitanium complexes are highly face-selective.

Stereopentads can be obtained from *meso*-dialdehydes by treatment with (*R*,*R*)-**II** and (*S*,*S*)-**II**. For example, when *meso*-dialdehydes **21** and **30** were treated with (*R*,*R*)-**II**, the stereopentads **29** and **32** were isolated after reduction of the intermediate lactols **28** and **31** with $NaBH_4$ (Fig. 9) [40]. It is worth noting that compound **32** corresponds to the C15–C21 fragment of (+)-discodermolide (Fig. 10). The desymmetrization of *meso*-dialdehydes by using chiral titanium complexes allows a short and efficient synthesis of polypropionates.

As the chiral allyl- and crotyltitanium complexes can tolerate a great number of functionalities, they can be used efficiently in the synthesis of biologically active natural products. For our part, we choose to synthesize (+)-discodermolide as we have already obtained the C15–C21 fragment. (+)-Discodermolide is a unique polyketide isolated from the Caribbean deep-sea sponge *Discodermia Dissoluta* [41, 42]. Its structure was determined by extensive spectroscopic studies and the relative stereochemistry was assigned by single crystal X-ray crystallography. Structurally, it bears 13 stereogenic centres, a tetrasubstituted γ-lactone (C1-C5), one di- and one trisubstituted (*Z*)-double bond, a pendant carbamate moiety (C19) and a terminal (*Z*)-diene (C1-C24). (+)-Discodermolide was initially found to be a potent immunosuppressive agent, both in vivo and in vitro, as well as displaying antifungal activity. It inhibited T-cell proliferation with an IC_{50} of 9 nM and graft versus host disease in transplanted mice. Further biological screening of this com-

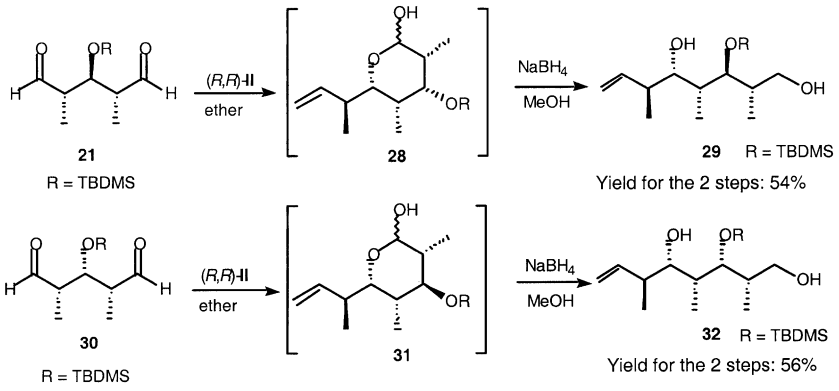

Fig. 9. Synthesis of stereopentads by desymmetrization of *meso* dialdehydes.

pound revealed cytotoxicity, causing cell cycle arrest in the G2/M phase in a variety of human and murine cell lines [43]. (+)-Discodermolide has been recognized as one of the most potent tubulin polymerising agents presently known. The highly encouraging biological profile of (+)-discodermolide makes it a promising candidate for clinical development as a chemotherapeutic agent for taxol-resistant breast, ovarian and colon cancer and other multidrug-resistant cancers. Clinical development is severely hampered by the extremely scarce supply of (+)-discodermolide (0.0002% w/w frozen sponge) from the natural source. Thus, total synthesis presently provides the only viable route to useful quantities of this novel cytotoxic polyketide. Consequently, there has been considerable synthetic effort toward (+)-discodermolide.

Our approach to (+)-discodermolide is based on synthesis of two fragments **G** and **H** by using allyltitanations. Connection of **G** and **H** will then have to be carried out with the help of a palladium-catalyzed coupling reaction (Fig. 10).

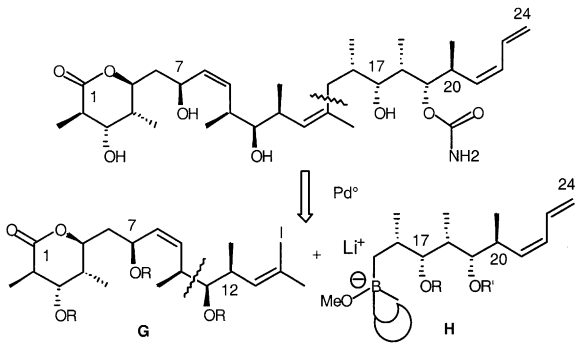

Fig. 10. Retrosynthetic analysis of (+)-discodermolide.

The synthesis of fragment C15–C24 was achieved from *meso*-dialdehyde **30**, which was transformed to iodide **33** in 8 steps via stereopentad **32**. The synthesis of the C1–C13 fragment was achieved in 18 steps from the commercially available methyl (+)-3-hydroxy-2-methyl propionate **35**, the stereogenic centre of which corresponds to C12 of (+)-discodermolide. All the stereogenic centres were controlled by using (*R,R*)-**I** (C7) and (*R,R*)-**II** (C2, C3, C4, C5, C11, C12) (Fig. 11).

The transformation of **33** to the boronate **34** and the coupling of this later compound with the vinyl iodide of type **G**, prepared from **45**, will lead to the C1-C24 fragment of (+)-discodermolide. The stereocontrolled synthesis of compounds **33** and **45** demonstrates that

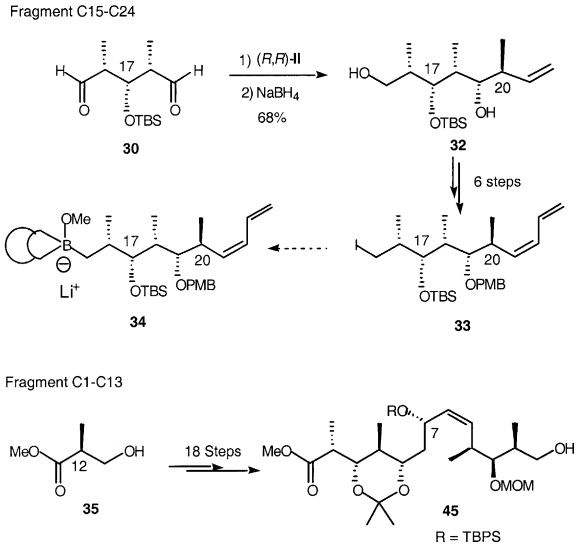

Fig. 11. Synthesis of the C1-C13 and C15-C24 fragments of (+)-discodermolide.

the highly face selective allyltitanium complexes are useful reagents for achieving remote stereocontrol in acyclic systems. Furthermore, by using these reagents, protection-deprotection sequences can be avoided as polar groups are tolerated, which increases the efficiency of the syntheses.

Acknowledgements

The COST program D13/001/00 is acknowledged for support and Eli-Lilly (Indianapolis, IN) as well as PPG-Sipsy are acknowledged for financial support.

References

[1] R.W. Hoffmann, Angew. Chem., Int. Ed. Engl. 21 (1982) 555.
[2] Y. Yamamoto, K. Maruyama, Heterocycles 18 (1982) 357.
[3] R.W. Hoffmann, Angew. Chem., Int. Ed. Engl. 26 (1987) 489.
[4] D. Hoppe, Angew. Chem., Int. Ed. Engl. 23 (1984) 932.
[5] J. Mulzer, L. Kattner, A.R. Strecker, C.H. Schröder, J. Buschmann, C.H. Lehmann, P. Luger, J. Am. Chem. Soc. 113 (1991) 4218.
[6] Y. Yamamoto, N. Asao, Chem. Rev. 93 (1993) 2207.
[7] W.R. Roush, in: B.M. Trost (Ed.), Comprehensive Organic Synthesis, Vol. 2, Pergamon Press, 1991, p. 1.
[8] W.R. Roush, in: G. Houben-Weyl, Helmchen, R.W. Hoffmann, J. Mulzer, E. Schaumann (Eds.), Methods of Organic Chemistry E21b, Thieme, 1995, p. 1491.
[9] J.A. Marshall, Chem. Rev. 96 (1996) 31.
[10] E.J. Thomas, in: G. Helmchen, R.W. Hoffmann, J. Mulzer, E. Schaumann (Eds.), Houben-Weyl, Methods of Organic Chemistry, Vol E21b, Thieme, 1995, p. 1508.
[11] J.W. Faller, D.L. Linebarrier, J. Am. Chem. Soc. 111 (1989) 1937.
[12] J.W. Faller, J.A. John, M.R. Mazzieri, Tetrahedron Lett. 30 (1989) 1769.
[13] J.W. Faller, M.J. Di Verdi, J.A. John, Tetrahedron Lett. 32 (1991) 1271.
[14] B. Weidmann, D. Seebach, Angew. Chem., Int. Ed. Engl. 22 (1983) 31.
[15] D. Seebach, B. Weidmann, L. Wilder, in: R. Scheffold (Ed.), Modern Synthetic Methods, Vol. 3, 1983, p. 217.
[16] D. Seebach, A.K. Beck, M. Schiess, L. Widler, A. Wonnacott, Pure Appl. Chem. 55 (1983) 1807.
[17] M.T. Reetz, in: F.L. Boschke (Ed.), Topics in Current Chemistry, 106, Springer, 1982, p. 3.
[18] M.T. Reetz, Pure Appl. Chem. 57 (1985) 1781.
[19] M.T. Reetz, Organotitanium Reagents in Organic Synthesis, Springer, Berlin, 1986.
[20] M. Riediker, R.O. Duthaler, Angew. Chem., Int. Ed. Engl. 28 (1989) 494.
[21] R.O. Duthaler, A. Hafner, M. Riediker, Pure Appl. Chem. 62 (1990) 631.
[22] A. Hafner, R.O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, J. Am. Chem. Soc. 114 (1992) 2321.
[23] R.O. Duthaler, A. Hafner, Chem. Rev. 92 (1992) 807.
[24] M.R. Jirousek, J.R. Gillig, C.M. Gonzalez, W.F. Heath, J.H. McDonald III, D.A. Neel, C.J. Rito, U. Singh, L.E. Stramm, A. Melikian-Badalian, M. Baevsky, L.M. Ballas, S.E. Hall, L.L. Winneroski, M.M. Faul, J. Med. Chem. 39 (1996) 2664.
[25] M.R. Jirousek, J.R. Gillig, D.A. Neel, C.J. Rito, D. O'Bannon, W.F. Heath, J.H. McDonald III, M.M. Faul, L.L. Winneroski, A. Melikian-Badalian, M. Baevsky, L.M. Ballas, S.E. Hall, Bioorg. Med. Chem. Lett. 5 (1995) 2093.
[26] M.M. Faul, L.L. Winneroski, C.A. Krumrich, K.A. Sullivan, J.R. Gillig, D.A. Neel, C.J. Rito, M.R. Jirousek, J. Org. Chem. 63 (1998) 1961.
[27] J. Cossy, S. Bouzbouz, J.-C. Caille, Tetrahedron: Asymmetry 10 (1999) 3859.
[28] T. Rosen, C.H. Heathcock, Tetrahedron 42 (1986) 4909.
[29] T. Oishi, T. Nakata, Synthesis (1990) 635.
[30] T. Hiyama, G.B. Reddy, T. Minami, T. Hanamoto, Bull. Chem. Soc. Jpn 68 (1995) 350.
[31] S. Bouzbouz, J. Cossy, Org. Lett. 2 (2000) 501.
[32] S. BouzBouz, J. Cossy, Tetrahedron Lett. 44 (2003) 4471.
[33] R.W. Hoffmann, Angew. Chem., Int. Ed. Engl. 26 (1987) 489.
[34] D. O'Hagen, in: E. Horwood (Ed.), The Polyketide Metabolites, Chichester, 1991.
[35] D.D. Schummer, B. Böhlendorf, M. Kiffe, G. Höfle, in: K. Kroh, H.A. Kirst, H. Maag (Eds.), Antibiotics and Antiviral Compounds, VCH, Weinheim, 1993.
[36] D. O'Hagen, Nat. Prod. Rep. 12 (1995) 1.
[37] C.J. Dutton, B.J. Banks, C.B. Cooper, Nat. Prod. Rep. 12 (1995) 165.
[38] S. Bouzbouz, M.E. Popkin, J. Cossy, Org. Lett. 2 (2000) 3949.
[39] J. Cossy, S. Bouzbouz, unpublished results.
[40] S. Bouzbouz, J. Cossy, Org. Lett. 3 (2001) 3995.
[41] S.P. Gunasekera, M. Gunasekera, R.E. Longley, G.K. Schulte, J. Org. Chem. 56 (1991) 1346.
[42] S.P. Gunasekera, S.A. Pomponi, R.E. Longley, US Patent No. US 5840750 (Nov 24) 1998.
[43] E. Haar, R.J. Kowalski, E. Hamel, C.M. Lin, R.E. Longley, S.P. Gunasekera, H.S. Rosenkranz, B.W. Day, Biochemistry 35 (1996) 243.