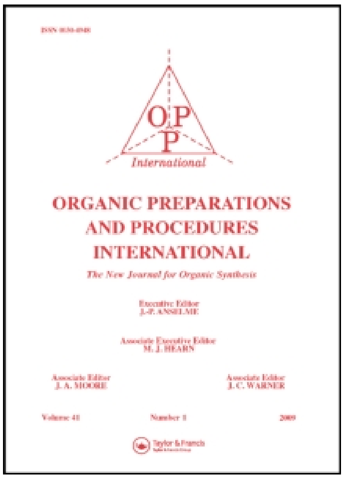


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

STEREOCHEMISTRY OF THE ALKYLATION OF LACTONES. A REVIEW

Malika Ibrahim-Ouali[a]; Jean-Luc Parrain[a]; Maurice Santelli[a]
[a] ESA au CNRS n° 6009, Centre de St-Jérôme, Marseille Cedex 20, FRANCE

To cite this Article Ibrahim-Ouali, Malika , Parrain, Jean-Luc and Santelli, Maurice(1999) 'STEREOCHEMISTRY OF THE ALKYLATION OF LACTONES. A REVIEW', Organic Preparations and Procedures International, 31: 5, 467 — 505

To link to this Article: DOI: 10.1080/00304949909355335

URL: http://dx.doi.org/10.1080/00304949909355335

ORGANIC PREPARATIONS AND PROCEDURES INT., 31 (5), 467-505 (1999)

STEREOCHEMISTRY OF THE ALKYLATION OF LACTONES. A REVIEW

Malika Ibrahim-Ouali, Jean-Luc Parrain and Maurice Santelli*

ESA au CNRS n° 6009, Centre de St-Jérôme, 13397 Marseille Cedex 20, FRANCE

STEREOCHEMISTRY OF THE ALKYLATION OF LACTONES. A REVIEW

Malika Ibrahim-Ouali, Jean-Luc Parrain and Maurice Santelli*

ESA au CNRS n° 6009, Centre de St-Jérôme, 13397 Marseille Cedex 20, FRANCE

GLOSSARY OF ABBREVIATIONS AND INTRODUCTION

Bz	benzoyl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
Cbz	benzyloxycarbonyl
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
HMPA	hexamethylphosphoric triamide
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
LIPC	lithium isopropylcyclohexylamide
MOM	methoxymethyl ether
NaHMDS	sodium hexamethyldisilazane
St	steroid
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Tr	triphenylmethyl
Ts	*p*-toluenesulfonyl

The references are given on the right-hand side of the equations.

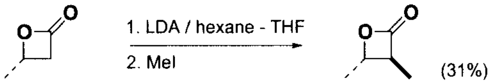
The lactone moiety is present in a wide variety of natural products and their analogs which exhibit diverse biological activities. Furthermore, simple lactones have been used as intermediates for the synthesis of biologically active compounds. Alkylation of lactones has become a very useful reaction and due to the known relationship between the biological activity of a molecule and its absolute configuration; thus there is a necessity to obtain these lactones in a pure stereochemical form. The present review reports the alkylation of a variety of β-, γ-, δ- and ε-lactones and the observed stereochemistry.

We have to note here that there are no references in this review prior to 1980. Indeed, although studies on the alkylation of lactone enolates were conducted throughout the 1970's, the majority of these examples[1-4] give no information about the stereochemistry. Thus, the focus of this review will be on the more recent results.

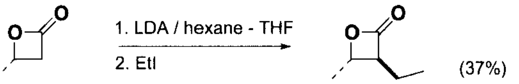
I. ALKYLATION OF β-LACTONES (β-Propiolactones)

In general, the alkylation of 3-substituted β-lactones gives the *trans*-product with good stereoselectivity.

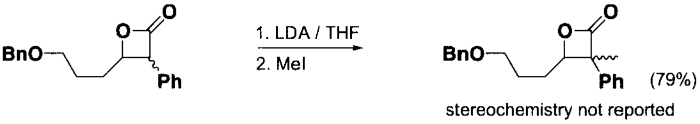
Ref.



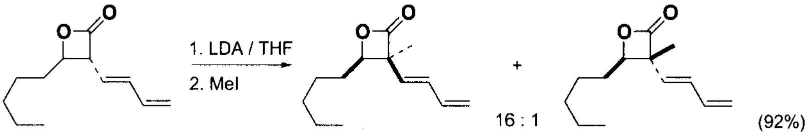
5



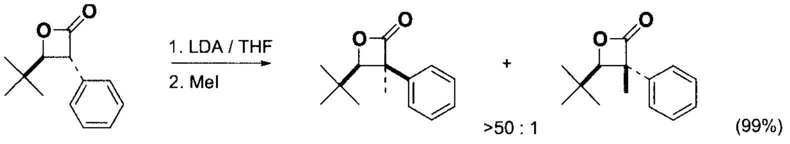
5



6

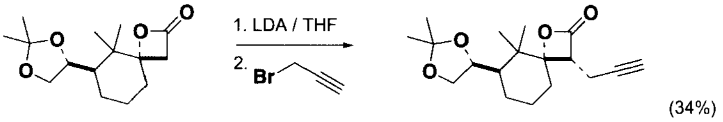


7



8

In the case of bicyclic β-lactones issue from ref. 9, propargylation reaction occurs only in anti position regarding the hindered *gem*-dimethyl carbon of the adjacent cycle.

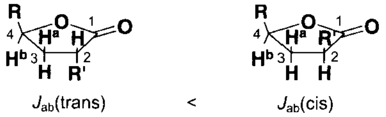


9

II. ALKYLATION OF γ-LACTONES (γ-Butyrolactones)

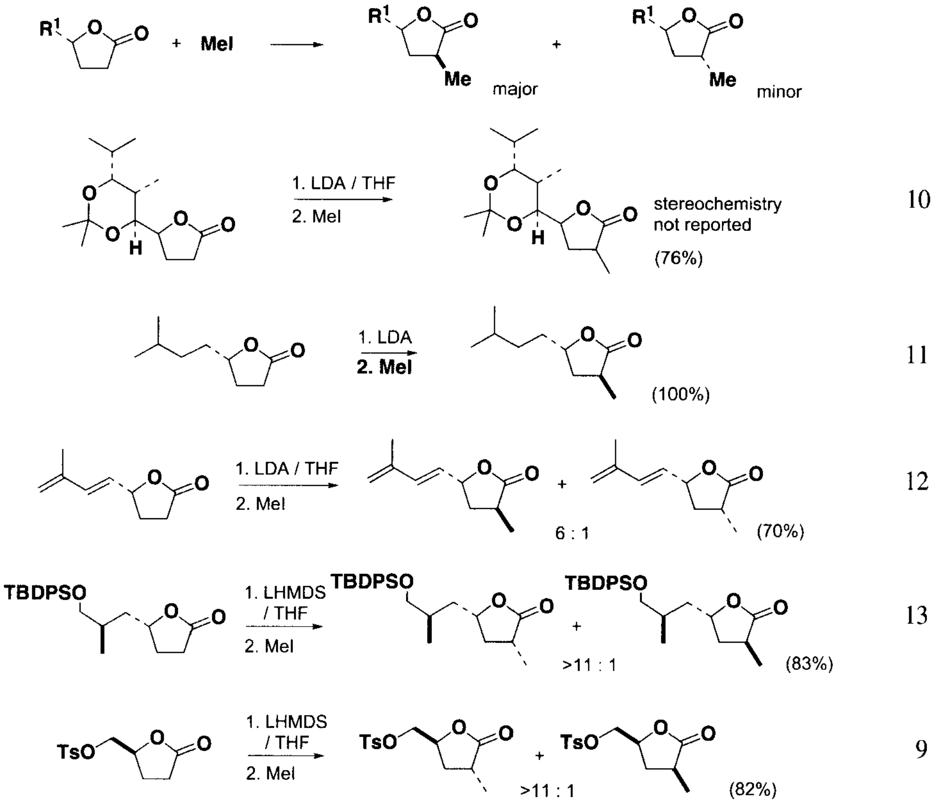
1. Alkylation of 4-Substituted γ-lactones

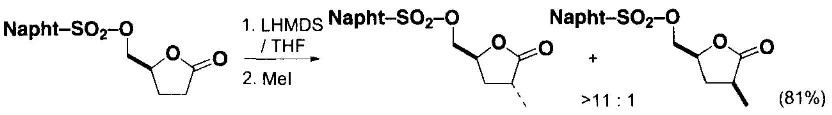
Alkylation of 4-substituted γ-lactones led to the *trans*-product as major isomer. The stereochemistry of the reaction depends of the nature of the substituent at C-4. The relative stereochemistry of these compounds can be easily assigned by NMR analysis, as reported by Menges and Coll. (ref. 53). Indeed, the coupling constants ($J_{3,4}$) between the methylene protons (H-3) and the methine proton (H-4) are characteristic. For *cis*-lactones (regarding at C-2 and C-4), the coupling constants between H-3 and H-4 are higher than those observed for *trans*-lactones. 13C NMR spectra present also signals which are characteristic of the *cis*- or *trans*-isomer. These NMR features are useful in the assignment of the relative configuration of the lactone.



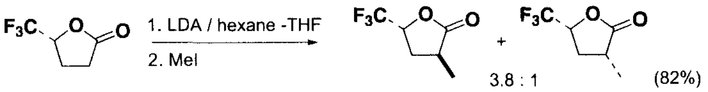
a. Methylation of 4-Substituted γ-lactones

The alkylation of 4-substituted γ-lactones led to the *trans* 2,4-disubstituted γ-lactones as major isomer with good or moderate stereoselectivity. α-Alkyl γ-lactones are in general synthesized *via* their enolates generated under hard basic conditions (for example, lithium dialkylamide as base). In this case, products are purified by chromatography on silica gel.

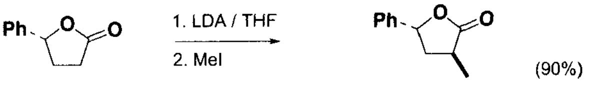




9

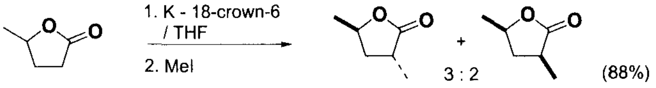


14



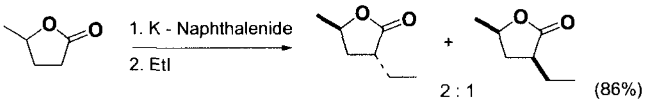
15

Jedlinski and co-workers have reported, in 1987, a novel and direct method to introduce α-substitution into γ-lactones by using a THF solution of potassium, containing K(–) anions and K(+) cations complexed by 18-crown-6. Deprotonation of the γ-lactone ring and formation of the lactone enolate take place by interaction with K(–) anions. The enolates could react with numerous alkyl halides to provide good yields of the corresponding α-substituted γ-lactones. However, the obtained stereoselectivities are lower than those obtained *via* lithium enolates.

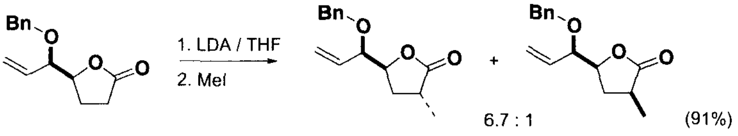


16

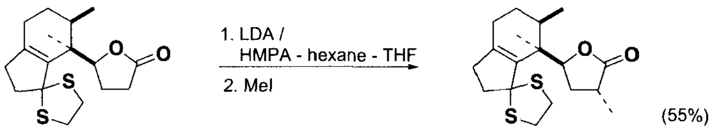
Later, the same authors reported the use of potassium naphthalenide in either the presence or the absence of crown-ether18-crown-6 to yield the lactone enolates. Nevertheless, the observed selectivities are not increased under these conditions.



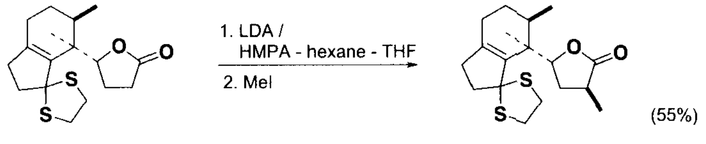
17



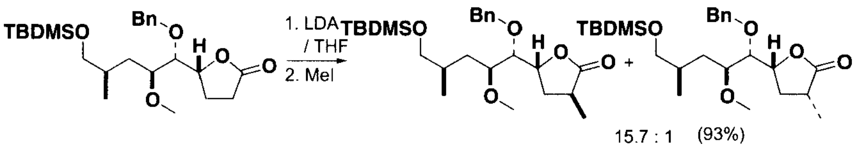
18



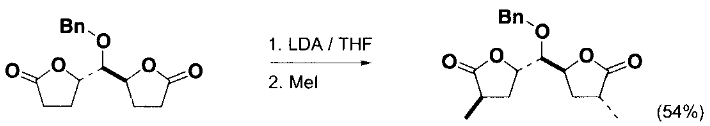
19



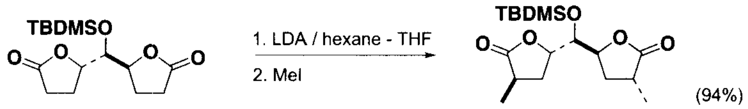
15



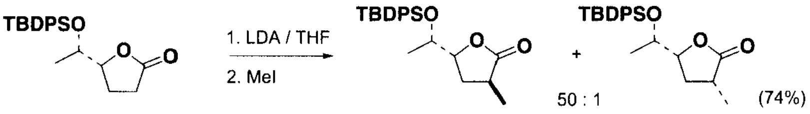
18



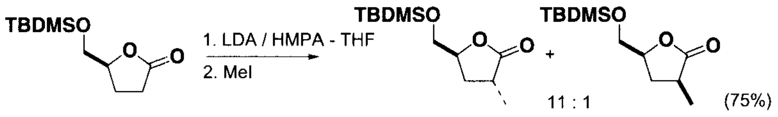
20



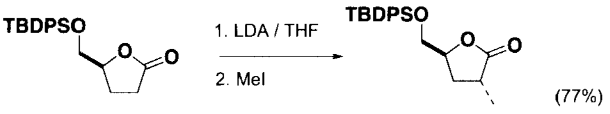
21



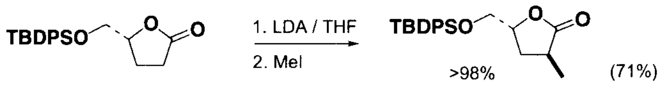
22



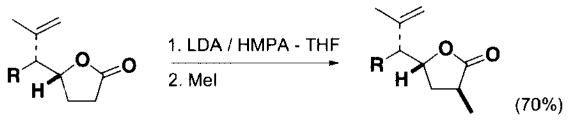
23



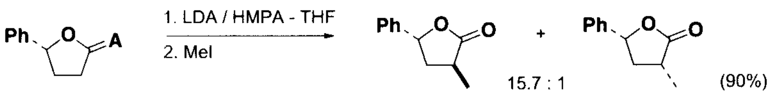
24



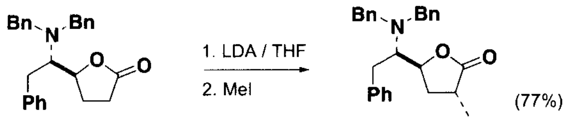
25



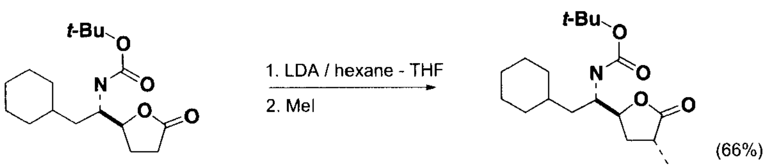
26



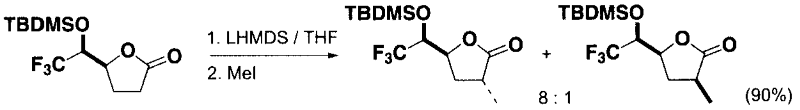
27



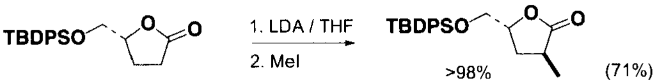
28



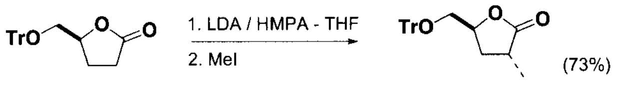
29
30



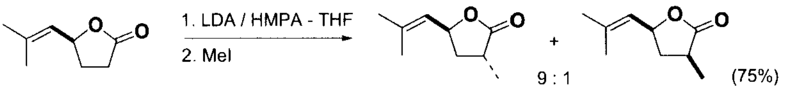
31



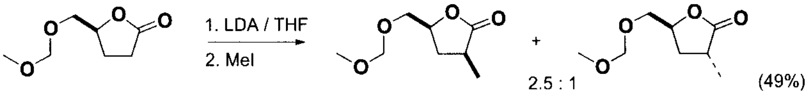
26



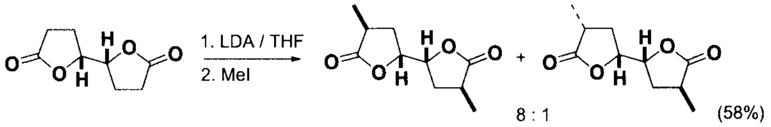
32
33
34
35



36

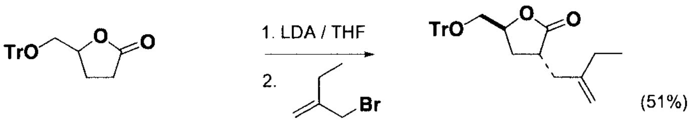


37

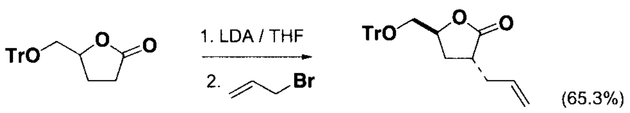


38

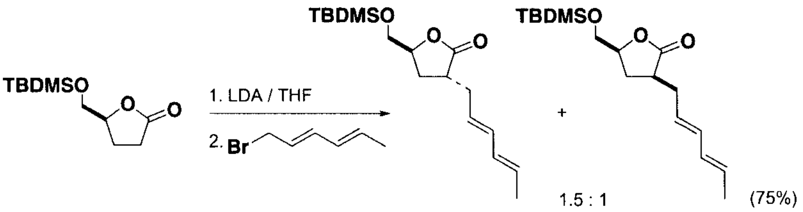
b. Allylation of 4-Substituted γ-lactones



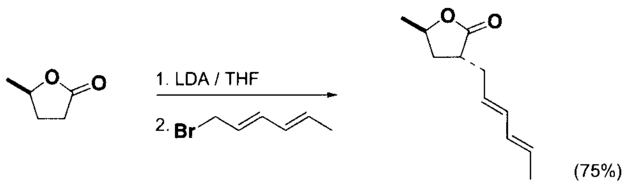
39



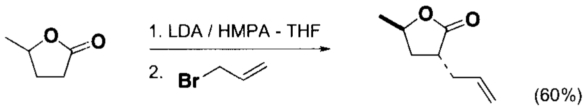
40
41
42
43



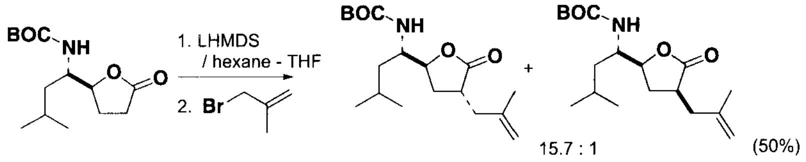
44



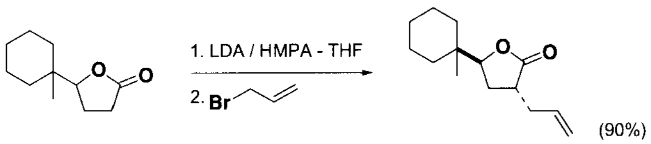
42



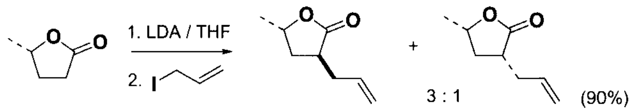
45



46

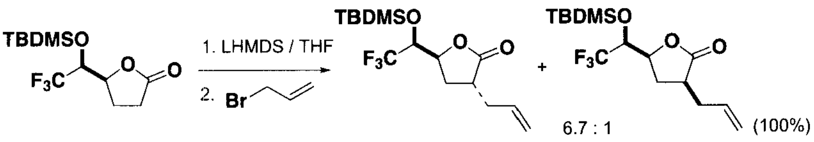


47

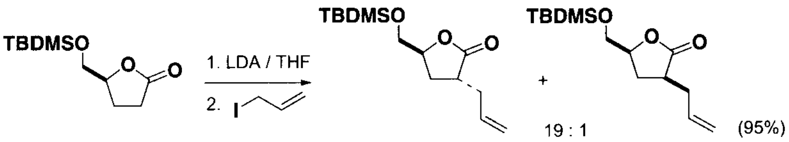


by decreasing the temperature, the ratio could be displaced to 19 : 1

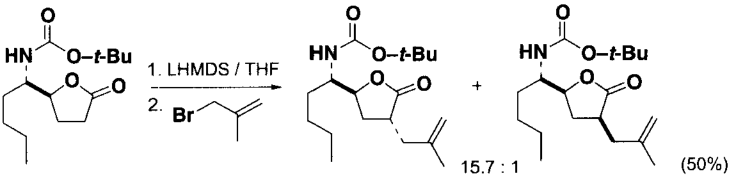
48



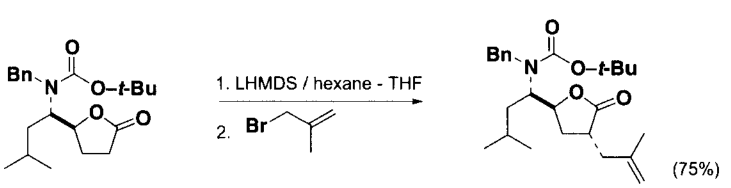
28



49

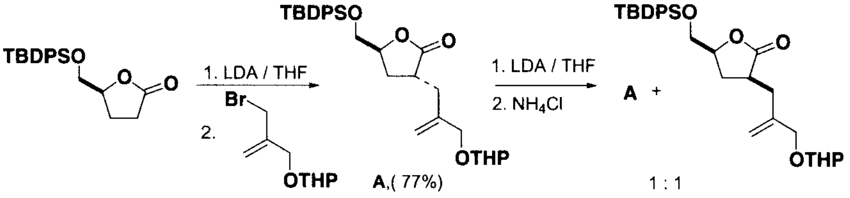


50
51

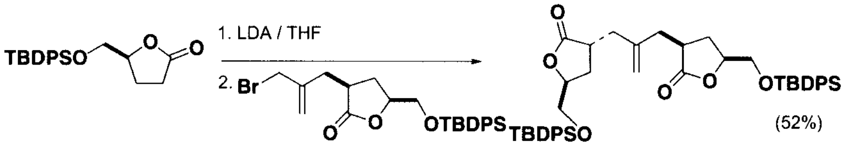


52

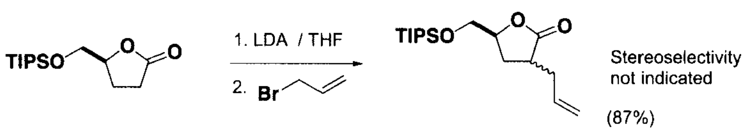
In the case of the lactone described by Brückner and co-workers (53), the alkylation of the lithium enolate proceeded with high *trans* selectivity as was predictable. By enolization and side-selective reprotonation, part of this material was epimerized to lactone *cis*.



53



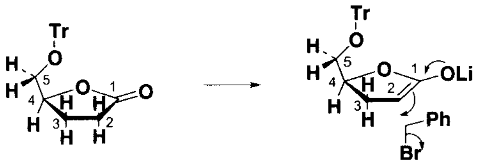
53

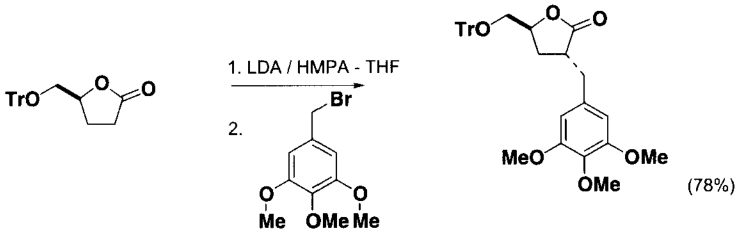


54

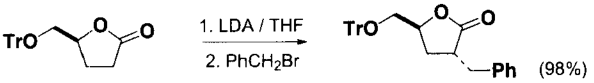
c. Benzylation of 4-Substituted γ-lactones

As above, the same remarks could be done for the benzylation of 4-substituted γ-lactones. The starting lactone has a specific conformation. Tamioka and co-workers (ref. 56) have made a conformational analysis of the starting lactone (R = CH_2-OTr at C-4) in $CDCl_3$ by using 400-MHz NMR spectroscopy. NMR studies revealed that coupling constants of 3.4 and 4.4 Hz between the methine proton (H-4) and methylene protons (H-5) of the trityloxymethyl group could explain the predominance of a preferred conformation for the molecule. The C-O bond of the bulky trityloxymethyl group is positioned *anti* to the C-(4)-H bond, an unexpected alignment considering the apparently unfavorable steric interactions present. It is also noteworthy that the coupling constants, 5.8 and 8.1 Hz, between H-4 and H-3 indicate that the trityloxymethyl group is located above the plane of γ-lactone ring. Attack of an electrophile from the β-face would encounter steric hindrance, didacting α-face entry of the alkylating agent. The rationalisation is based upon the assumption of a reactant-like transition state in the alkylation. The origin of the high stereoselectivity is attributed to a unique conformation of the starting molecule.

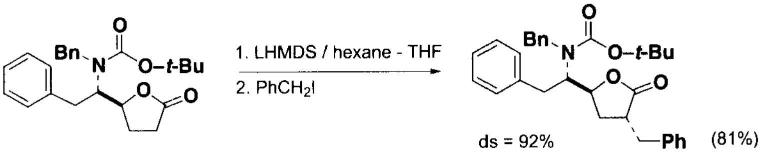




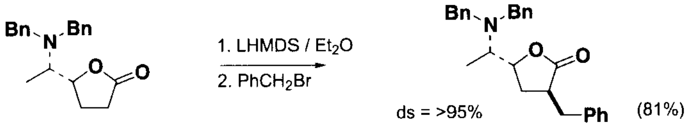
55



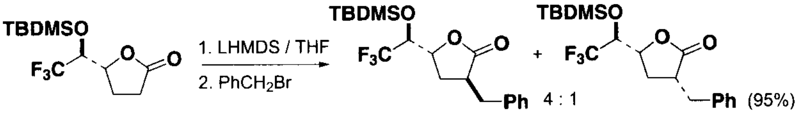
31
56



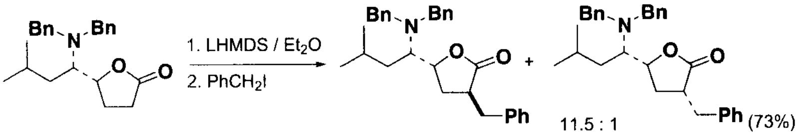
57
58



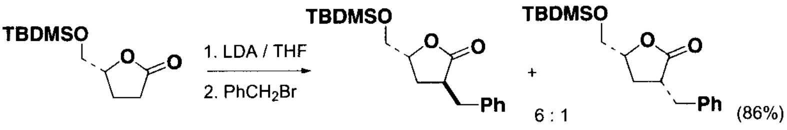
59
60



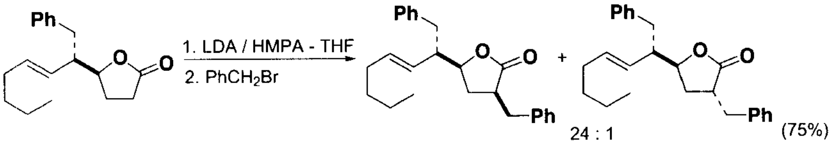
27
38



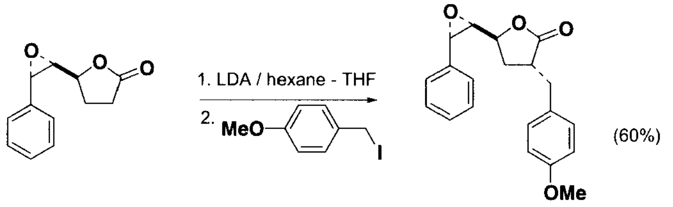
61



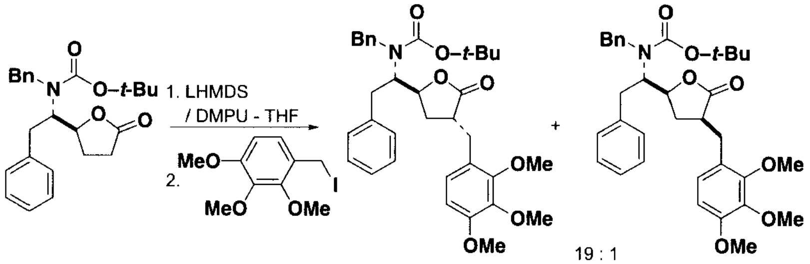
62



63



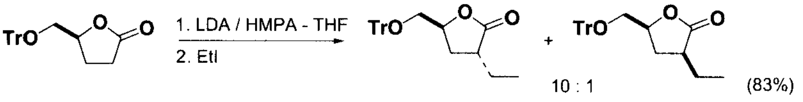
64



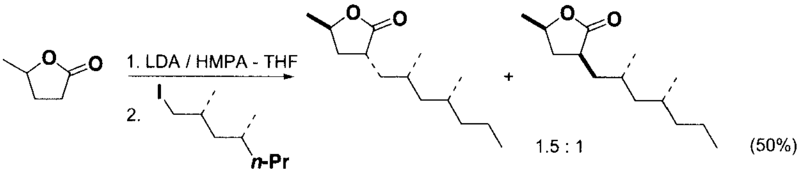
65

d. Alkylation of 4-Substituted γ-lactones

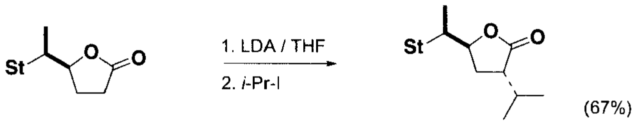
The *trans* lactone is the major isomer obtained by alkylation of 4-substituted γ-lactones.



38
48

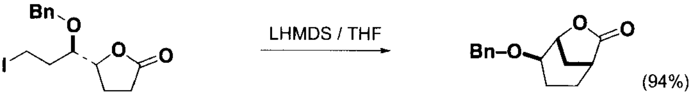


66

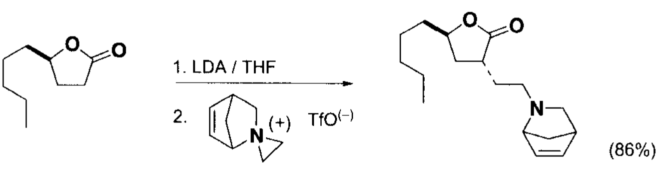


67

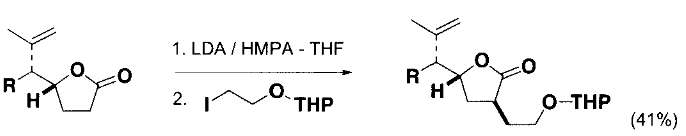
Rare are the examples of intramolecular alkylation described in the literature. Kotsuki and co-workers have reported one concerning a 4-substituted lactone by treatment with 1.2 equiv of LHMDS in THF to afford a bicyclic lactone in good yield. The stereochemical outcome of this alkylation is undoubtedly the *cis* orientation based on the structural constraints revealed by molecular model.



68



69

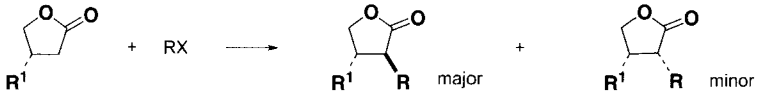


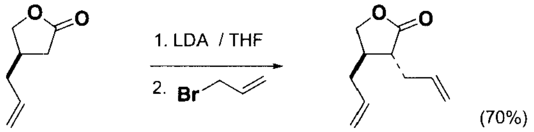
26

2. Alkylation of 3-Substituted γ-lactones

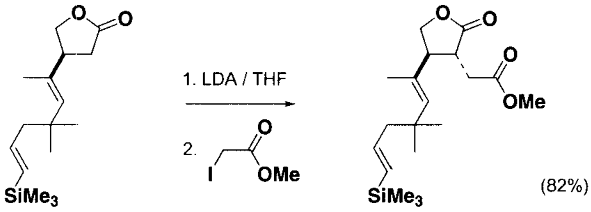
a. Alkylation of 3-Substituted γ-lactones

Good stereoselectivity is observed for the formation of 2,3-disubstituted γ-lactones. There are not a lot of examples described in the literature concerning the preparation of 2,3-disubstituted γ-lactones. The different authors obtained stereoselectively the *trans*-product. For example, Burke and Coll. (ref. 70) observed that lactone enolate alkylation with methyl iodoacetate stereoselectively proceeded to give the *trans*-disubstituted lactone with a good yield. This lactone is a precursor of (–)-pereniposin B which is representative of the drimane sesquiterpenes.

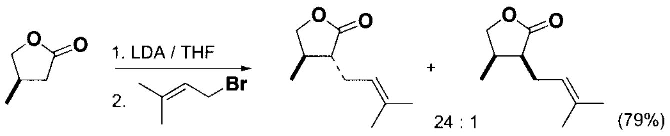




36



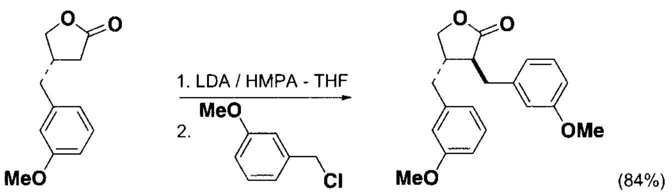
70



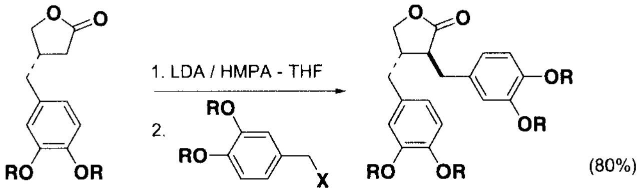
71

b. Benzylation of 3-Substituted γ-lactones

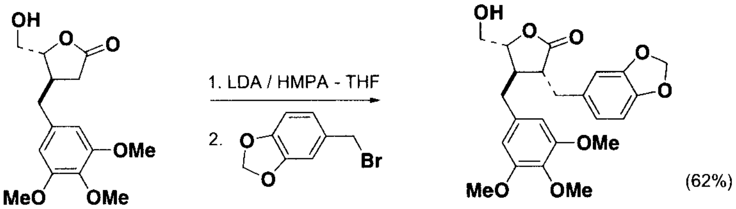
Benzyl condensation of enolates derived from the 3-substituted γ-lactones is highly stereo-controlled and leads to the *trans*-structures.



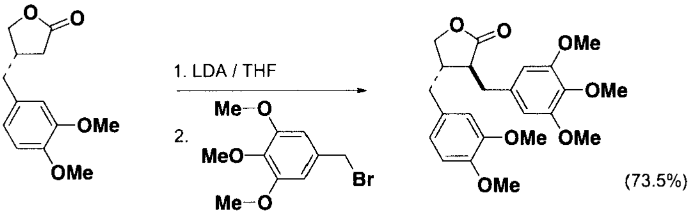
72
73
74



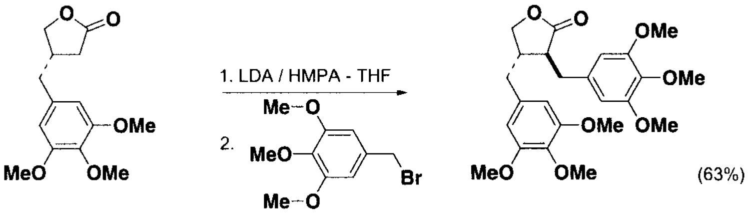
75-86



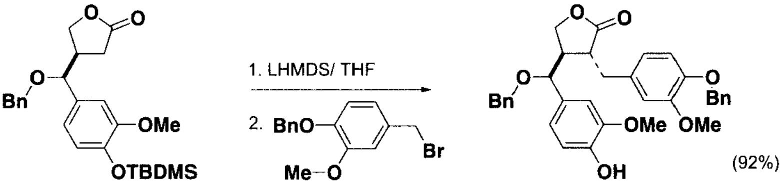
87
88



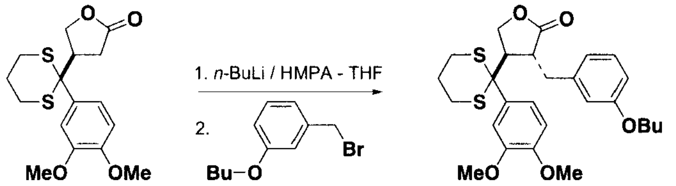
55
56
89
90
81



91
92
93



94

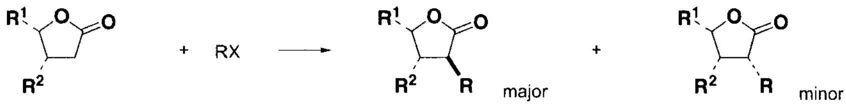


95
96

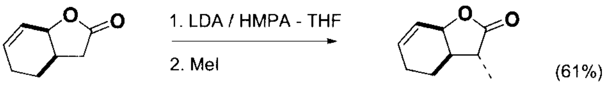
3. Alkylation of 3,4-Disubstituted γ-lactones

a. Methylation of 3,4-Disubstituted γ-lactones

i. Methylation of cis-3,4-Disubstituted γ-lactones

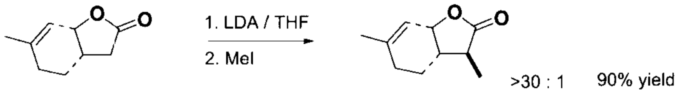


The stereochemistry of the alkylation is governed by the position of the substituent at C-3. The major product is the *trans*-lactone (*trans* regarding C-2 and C-3).

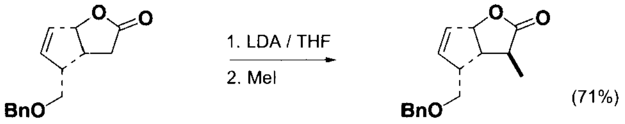


97

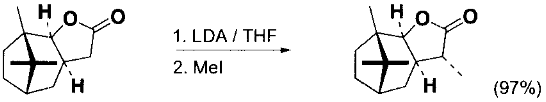
98



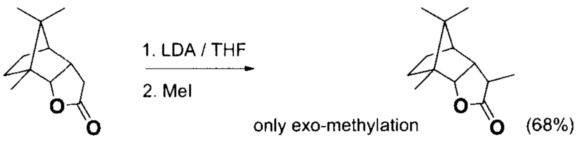
99



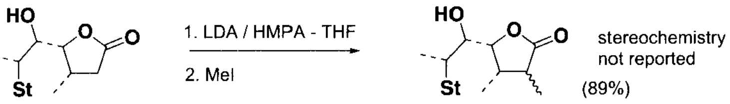
100



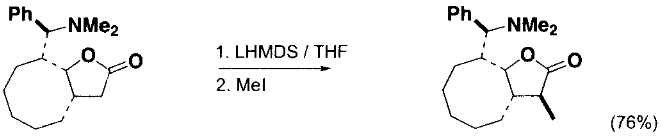
101



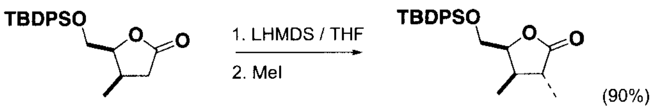
102



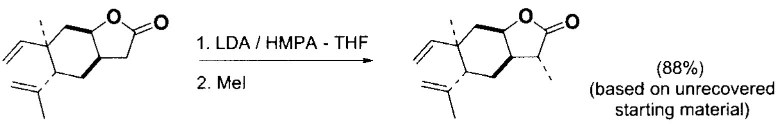
103



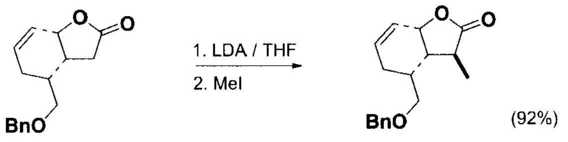
104



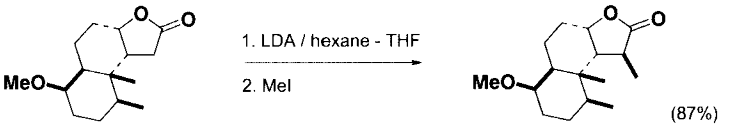
105



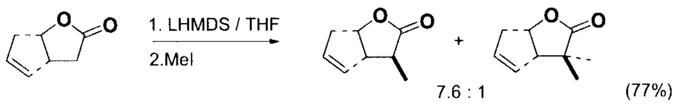
106



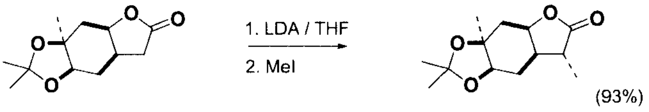
107



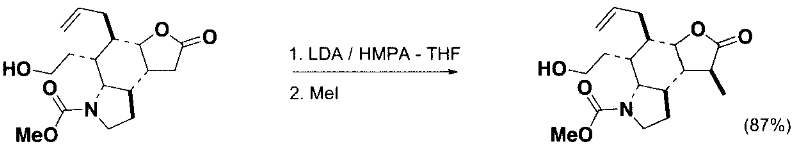
108



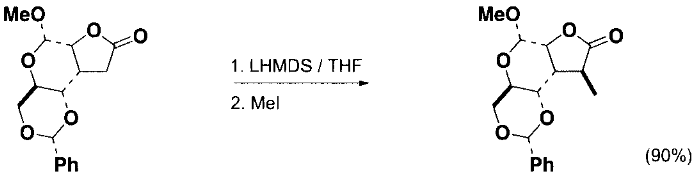
109
110



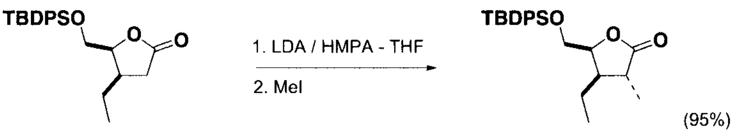
111



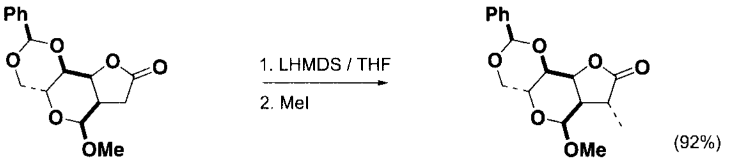
112
113



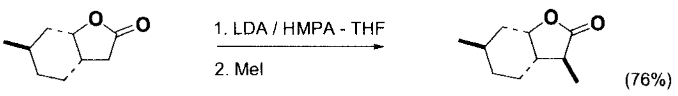
114



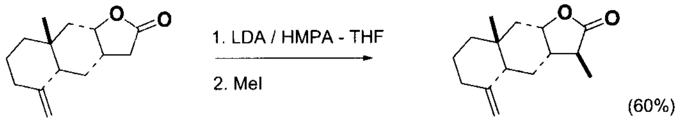
115



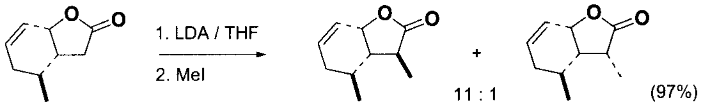
116



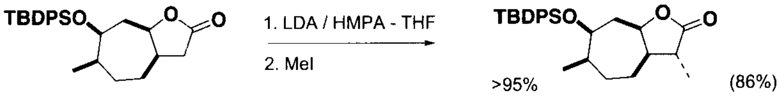
117



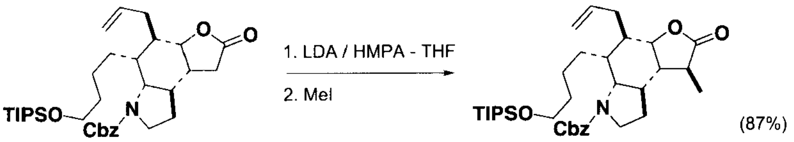
118



119

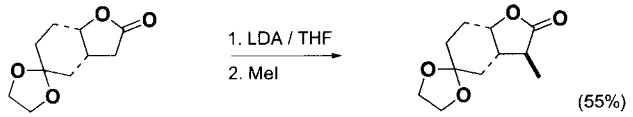


120



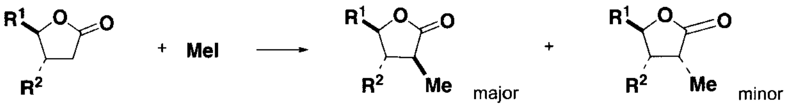
121

122

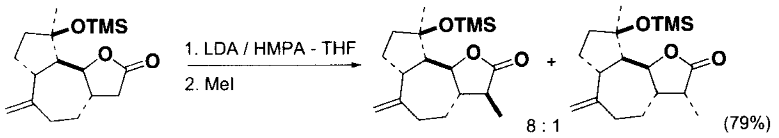


123

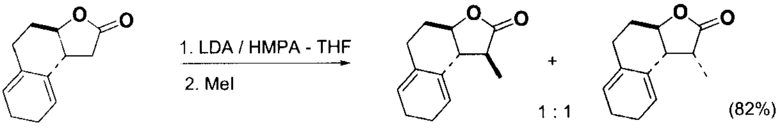
ii. Methylation of trans-3,4-Disubstituted γ-lactones



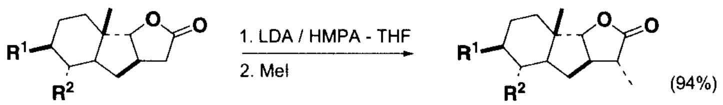
Here too, the *trans*-product regarding C-2 and C-3 is obtained preferentially. The stereochemistry of isomers is corroborated by means of tandem 2D COSY and NOE measurements or by X-ray analysis. In some cases, addition of HMPA in the reaction medium do not affect the stereochemical outcome though some acceleration of reaction rate is observed.



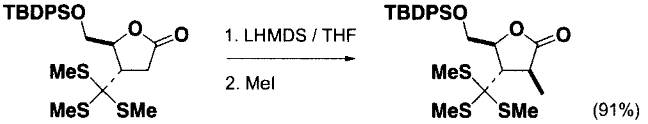
124
125



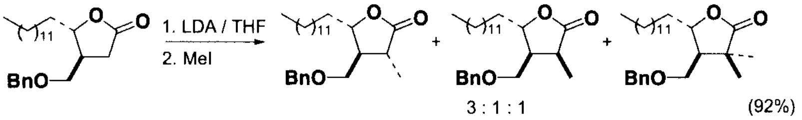
126



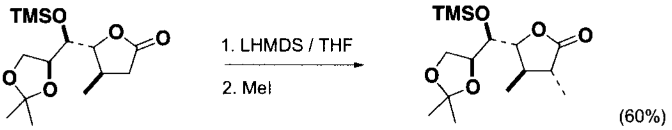
127



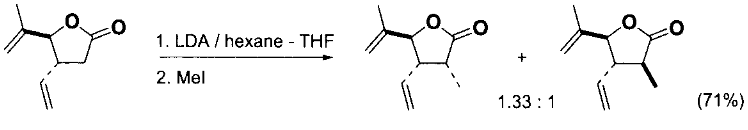
105



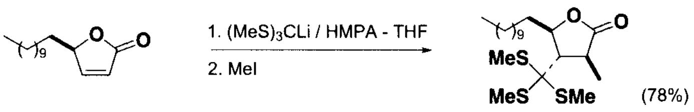
128



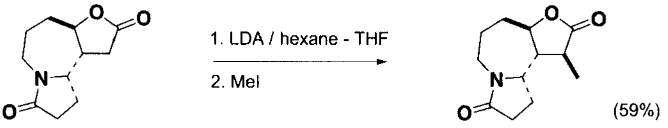
129



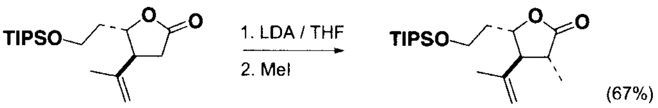
130



131

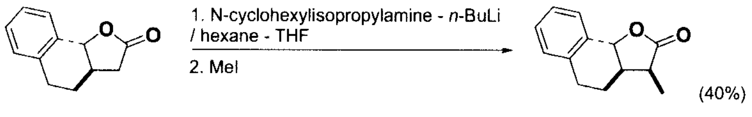


132



133

Contrary to the examples described before, Suzuki and Coll. (ref. 134) obtained, by treatment of their lactone with lithium isopropylcyclohexylamide followed by alkylation with methyl iodide, the formation of one isomer which is *cis* regarding at C-2 and C-3 (exo attack). The stereostructure of the lactone has been confirmed by NOE experiments. NOE between C(4)-H and the methyl group is observed.

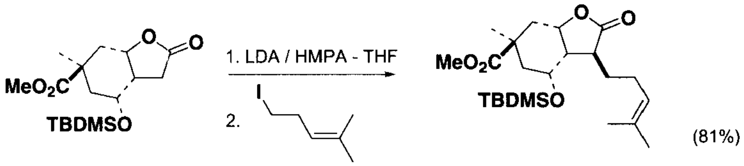


134

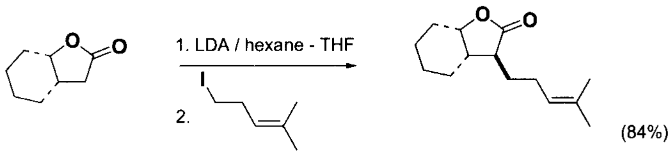
b. Alkylation of 3,4-Disubstituted γ-lactones

i. Alkylation of cis-3,4-Disubstituted γ-lactones

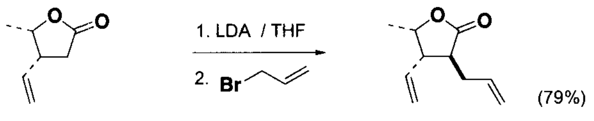
In the case of *cis* lactones, the different authors always observed the formation of only one product which is *trans* regarding at C-2 and C-3. Interesting to note that it is not the case when the stereochemistry of the starting lactone is *trans*.



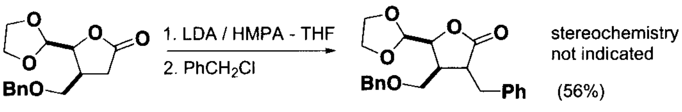
135



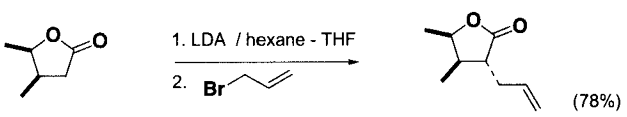
136
137



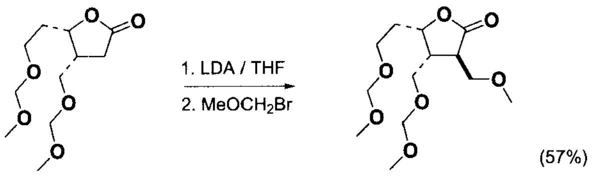
138



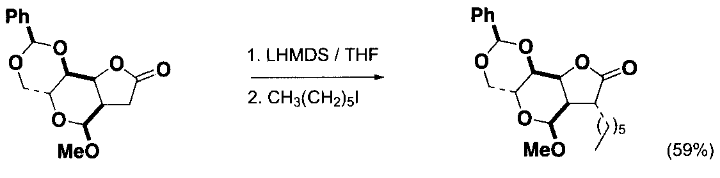
139



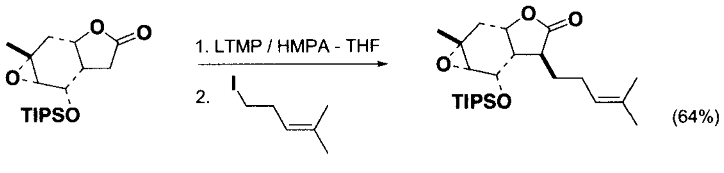
140



141



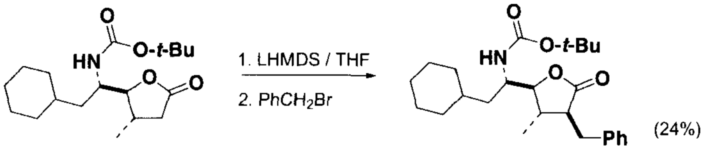
116



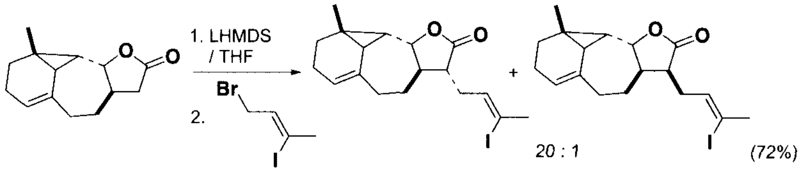
142

ii. Alkylation of trans-3,4-Disubstituted γ-lactones

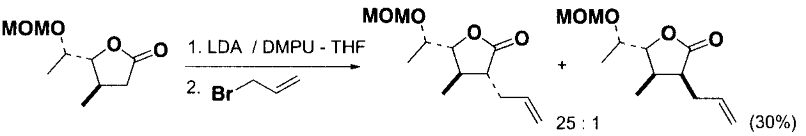
In the case of *trans*-3,4-disubstituted γ-lactones, the *cis*-product is the major isomer (*trans*: regarding C-2 and C-3). The relative configuration of the lactone can be determined by the spectral data. As reported by Radunz and Coll. (ref. 143), the configuration of the alkylation product is firmly established by the coupling constants $J_{H\text{-}2,H\text{-}3}$. Only traces of the *trans*-isomer can be detected and, generally, no amount of dialkylated material is formed. The high *cis*-stereoselectivity (regarding C-2 and C-4) of their lactone is explained by the transition state in which the front-side (*re*-side) of the lactone enolate is shielded by the methyl group, so that only backside (*si*-side) attack of the alkylation reagent occurs.



143



144



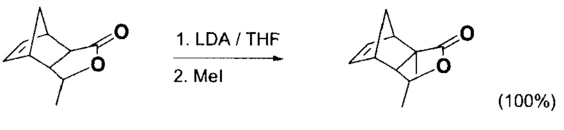
145

4. Alkylation of 2,3,4-Trisubstituted γ-lactones

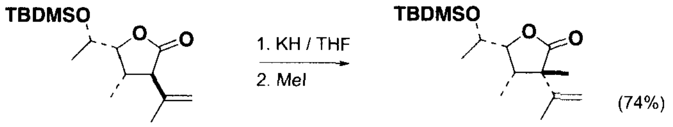
a. Methylation of 2,3,4-Trisubstituted γ-lactones

Yields and stereoselectivities are in most cases very good.

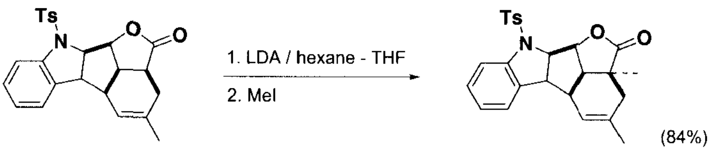
146



147

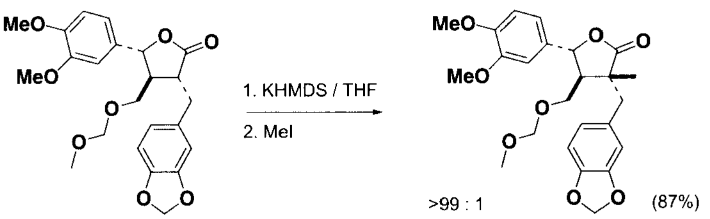


148



149

For the example described below, reported by Iwasaki and Coll., the potassium enolate was treated with MeI to furnish the corresponding lactone in a ratio of >99 : 1. The stereoselectivity observed in this reaction presumably originates from the conformational rigidity of the metal enolate induced by 1,3-allylic strain.

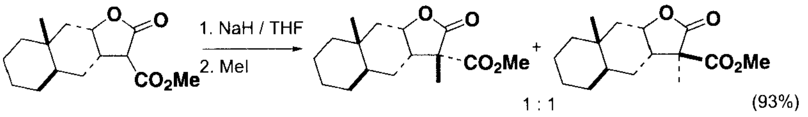


150
151

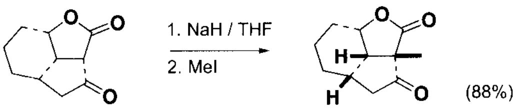
i. Methylation of β-Keto-3,4-Disubstituted γ-lactones

In some publications, the authors have done an activation of the α-position of the lactone by acetylation or methoxycarbonylation, affording the corresponding β-ketoester. So, "hard" conditions for the methylation are not necessary, NaH in THF or K_2CO_3 in acetone (ref. i) afforded the enolates.

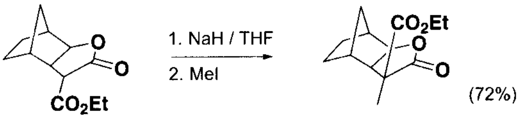
The stereoselectivity of the reaction respects the stereoelectronic principles. It is well known that γ-butyrolactone exists in two envelope forms which rapidly interconvert at room temperature. Adding substituents to the ring will shift the equilibrium depending on the energy differences between pseudo-axial and pseudo-equatorial positions. Enolates of the β-ketoesters derived from γ-butyrolactones also have two possible envelope forms in Newman projections. Both conformers can react by their α or β faces as reported by Lavallée and Coll. (ref. 158). The sterics requirements imposed by the electrophile determine the stereochemical outcome of the reaction.



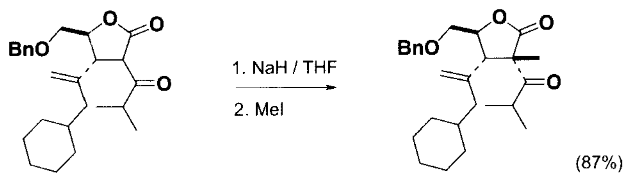
153



154

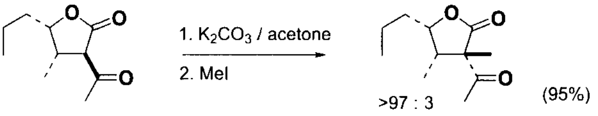


155

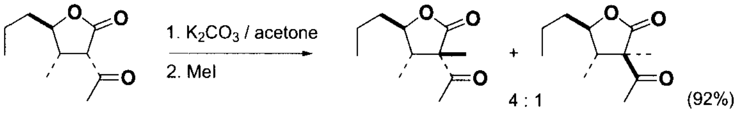


156

157

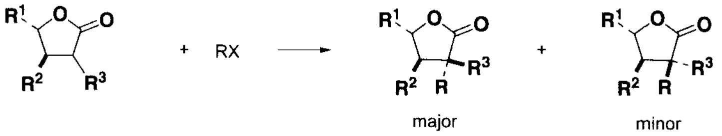


158

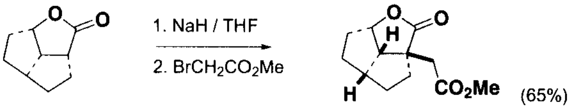


162

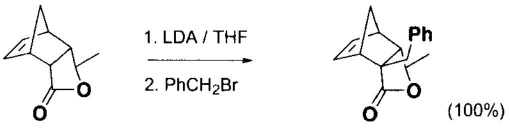
b. Alkylation of 2,3,4-Trisubstituted γ-lactones



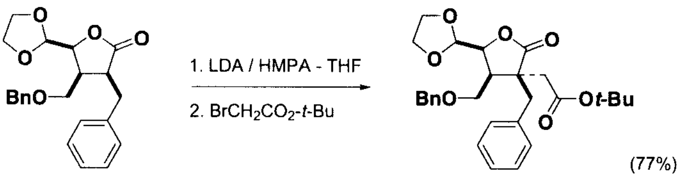
It is interesting to note and as we can predict, more is substituted the lactone and higher is the stereoselectivity. For trisubstituted and tetrasubstituted γ-lactones, the alkylation product obtained with an excellent selectivity, is often an intermediate in the synthesis of natural products such as pheromones, ionophores, lignans...



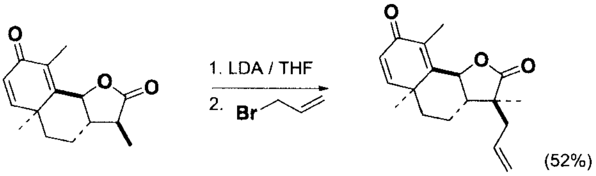
154



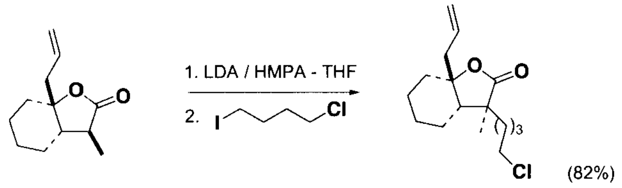
147



139

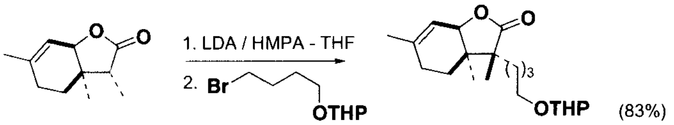


159

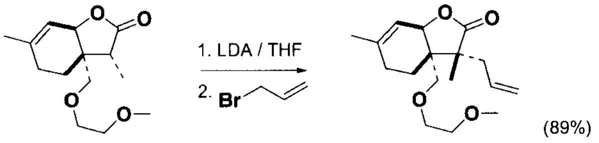


161

5. Alkylation of 2,3,3,4-Tetrasubstituted γ-Lactones

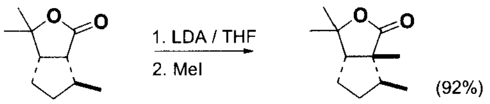


162

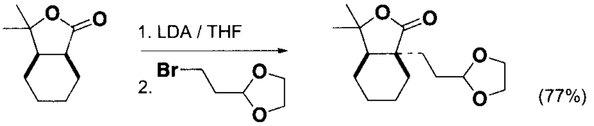


163

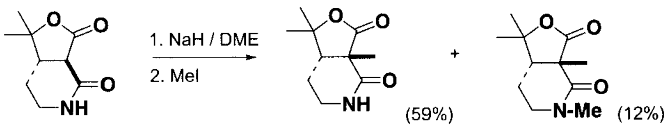
6. Alkylation of 2,3,4,4-Tetrasubstituted γ-lactones



164



165



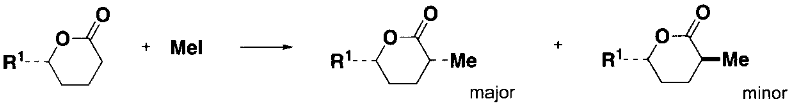
166

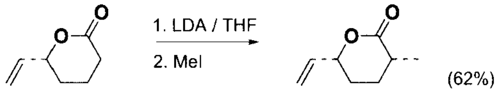
V. ALKYLATION OF δ-LACTONES (δ-Valerolactones)

The absolute configurations of the products obtained by alkylation of δ-lactones are, when it is possible, determined by correlation with optically pure substances. In the other cases, gas-liquid chromatography, HPLC, NMR spectra or X-ray analysis are used to determine the ratio of *cis/trans* and the stereochemistry of the alkylated lactones.

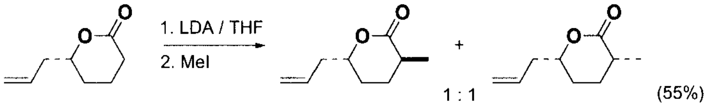
1. Methylation of 5-Substituted δ-lactones

The methylation of 5-substituted δ-lactones leads to the *cis*-lactone as major isomer with low stereoselectivity.

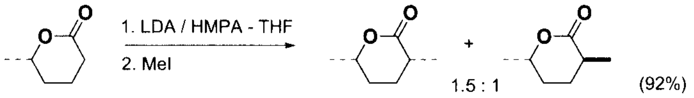




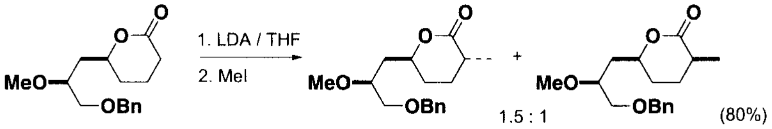
97



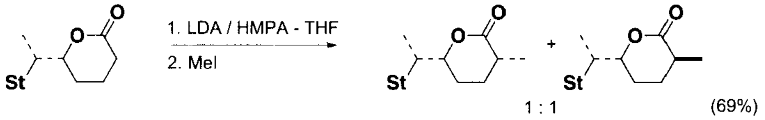
167



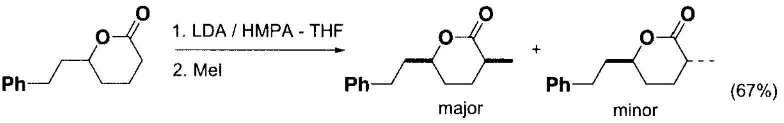
168



169



170
171

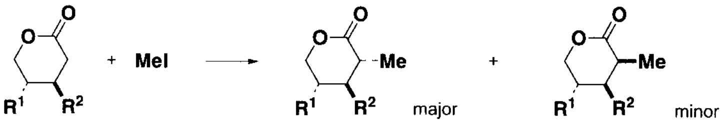


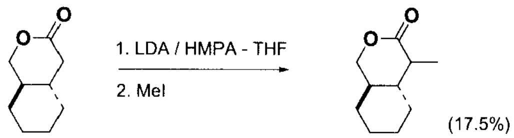
172

173

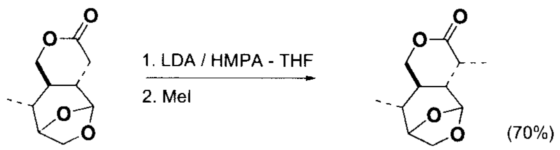
2. Methylation of 3,4-Disubstituted δ-lactones

There are not many examples reported in the literature concerning the methylation of 3,4-disubstituted δ-lactones.

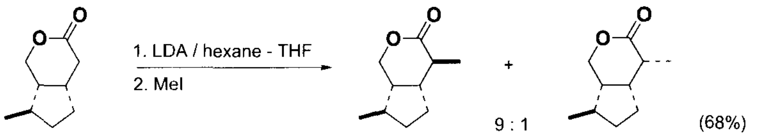




174



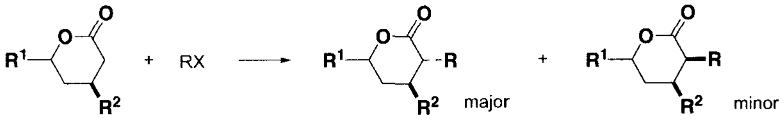
175

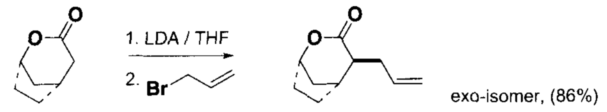


176
177
178

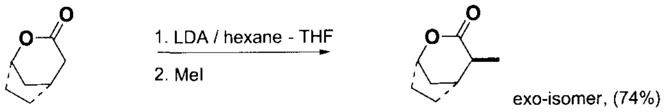
3. Alkylation of 3,5-Disubstituted δ-lactones

Stereoselectivities observed and yields are in general very good. When we look at the different examples described in the literature, the product obtained is the *trans*-isomer regarding at C-2, C-3. For example, treatment of the bicyclic lactone of Clive and co-workers (ref. 185) with 2 equiv of LDA followed by addition of alkyl iodide and HMPA gives the coupled product in good yield. The product is a single isomer with the stereochemistry at C-2 assigned on the basis of the proton coupling constant $J_{2,3}$ (3.0 Hz).

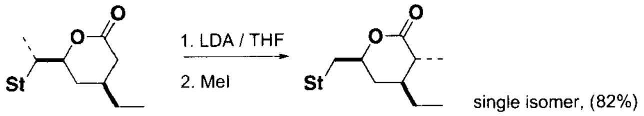




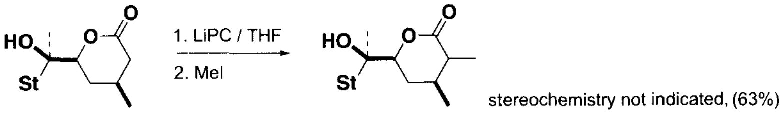
179



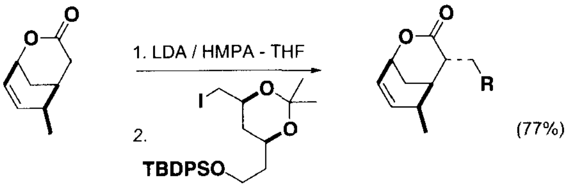
180
181
182



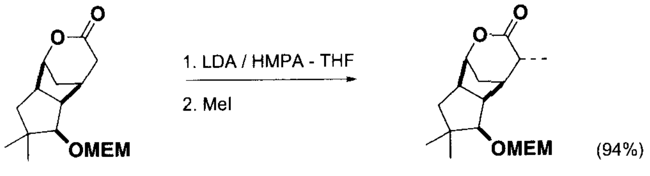
183



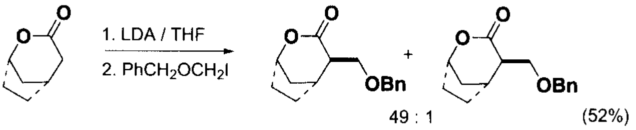
184



185



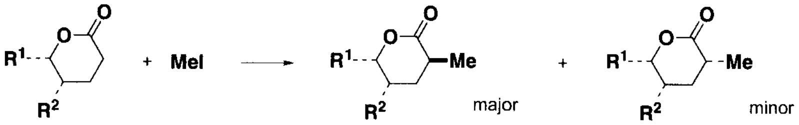
186



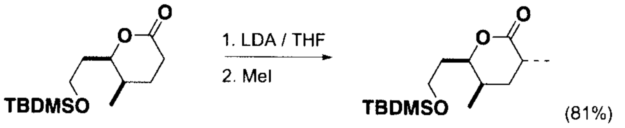
187

4. Methylation of 4,5-disubstituted δ-lactones

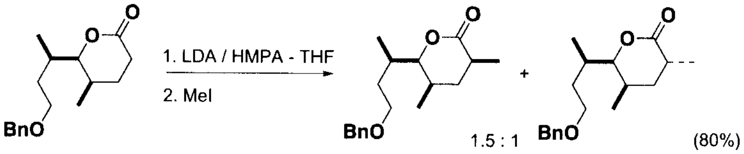
a. Methylation of cis-4,5-disubstituted δ-lactones



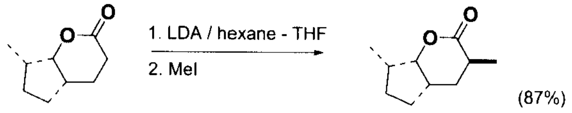
In contrast with 3,5-disubstituted δ-lactones, after methylation, two diastereoisomers are isolated, in general with an equimolar ratio. For the other cases, the major one is the *trans*-product regarding at C-2, C-4. Interesting to note that yields of this reaction are always good. Paquette and co-workers (190) observed only the formation of one stereoisomer, methylation of the enolate anion occurs only from the convex face of the molecule with good yield.



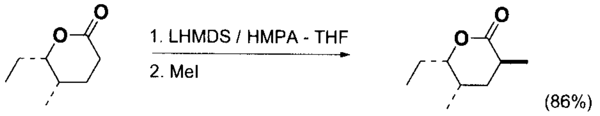
188



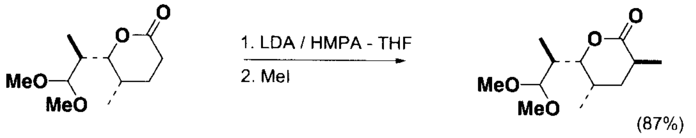
189



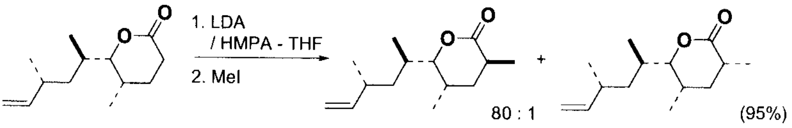
190



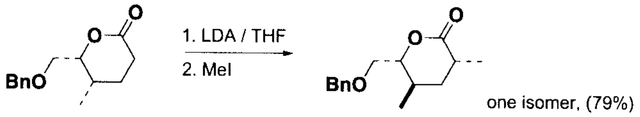
191



192

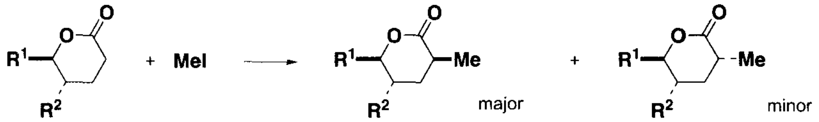


193

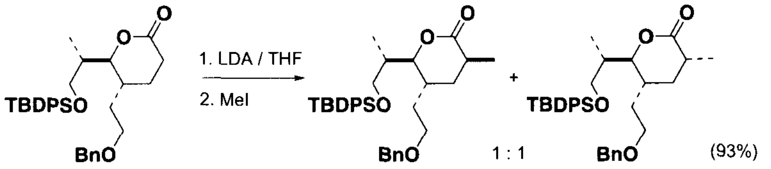


194

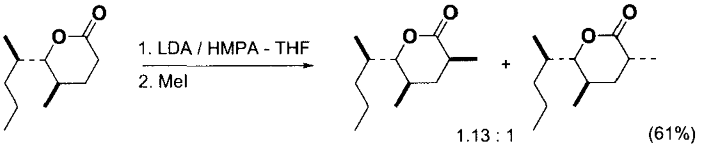
b. Methylation of trans-4,5-disubstituted δ-lactones



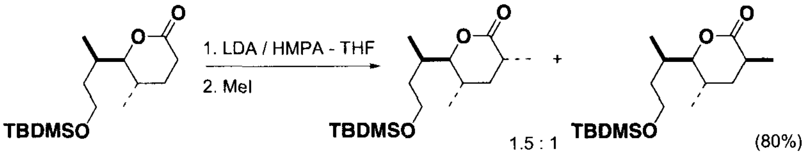
In all cases, a mixture of two diastereoisomers is obtained, and stereoselectivities are, in general, weak. Those lactones are often precursors of natural compounds, but, of course, there is only one of the two isomers which possess the required configuration. As reported by Mori and co-workers (ref. 201) methylation of their starting lactone afforded a mixture of the desired molecule (*trans* regarding C-2, C-4) and its isomer. This mixture is separable by preparative HPLC. The pure product is a precursor of pheromone. For the other examples, the separation of the two isomers has been done in the same manner.



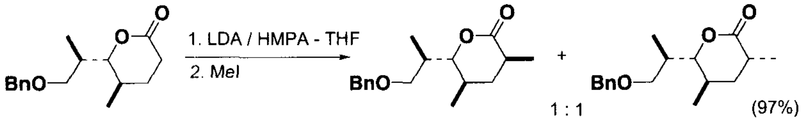
195



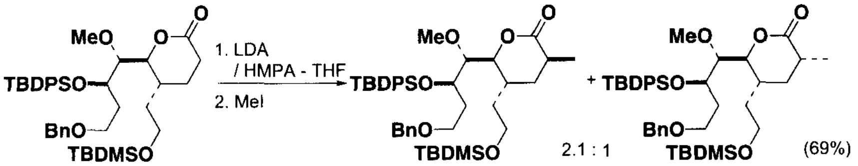
196
197



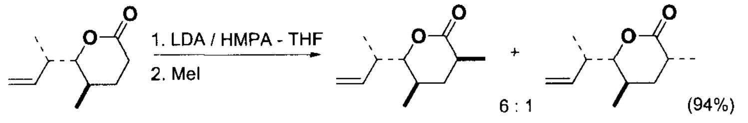
185



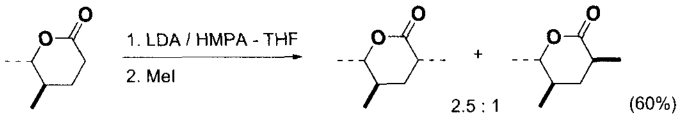
198



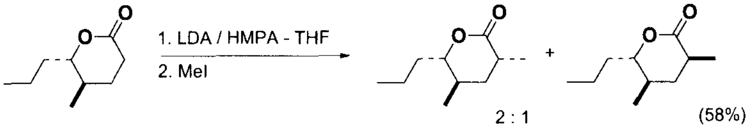
199



200



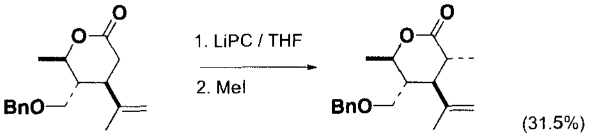
201



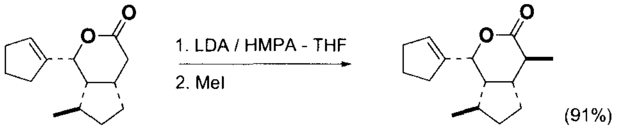
197

5. Methylation of 3,4,5-Trisubstituted δ-lactones

Only two examples are reported in the literature and in the two cases the authors observed the formation of a single isomer which is *trans* regarding at C-2, C-5.



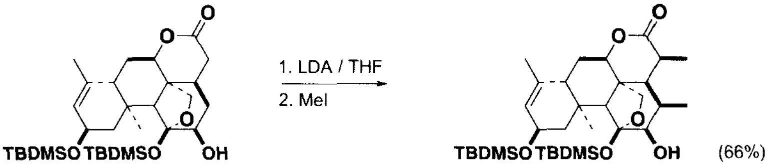
202



203

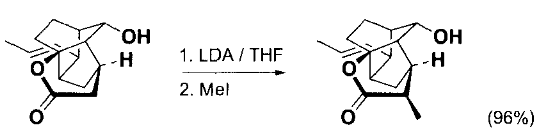
6. Methylation of 3,4,4,5-Tetrasubstituted δ-lactones

The sole example described in the literature is reported by Caruso and Coll. As indicated, they stereoselectively obtained one isomer with 66% yield in the synthesis of quasinoid analogs.

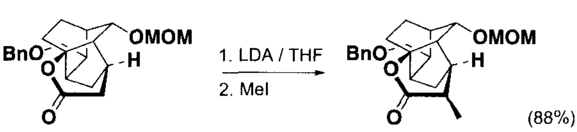


204

7. Methylation of 3,3,4,5,5-Pentasubstituted δ-lactones



205

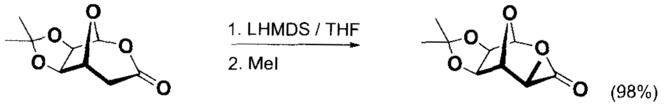


206

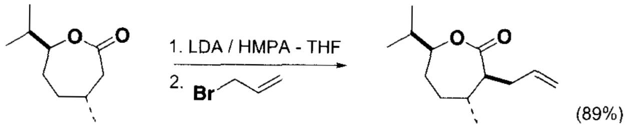
VI. ALKYLATION OF ε-LACTONES (ε-Caprolactones)

Only a few examples about the alkylation of ε-lactones are reported in the literature. In all cases, treatment of the starting lactone with a base and then with an alkyl halide led to one isomer with good to excellent yields.

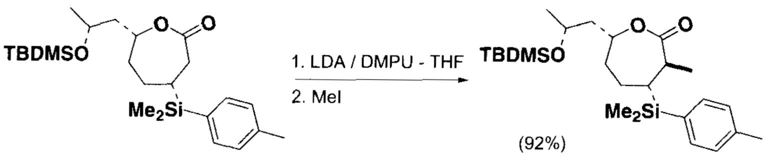
This reaction constitutes a key step for asymmetric total synthesis of azasugars described by Vogel *et al.* (ref. 207, 208).



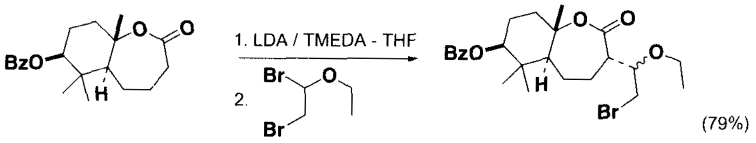
207
208



209



210



211

V. CONCLUSION

In summary, we have shown in this review that the stereochemistry of the product obtained by alkylation depends essentially on the nature, the size and the substituents already present on the starting lactone. The alkylated compounds can be useful building blocks for further synthetic applications. In some cases, this reaction is the key step for the synthesis of a natural product.

REFERENCES

1. G. H. Posner and G. L. Loomis, *Chem. Commun.*, 892 (**1972**).
2. P. A. Grieco and K. Hiroi, *ibid.*, 1317 (**1972**).
3. P. A. Grieco and M. Miyashita, *J. Org. Chem.* **39**, 120 (1974).
4. P. A. Grieco, *Synthesis* 67 (**1975**).
5. A. Griesbeck and D. Seebach, *Helv. Chim. Acta*, **70**, 1320 (1987).
6. K. T. Mead, H.-L. Yang, *J. Org. Chem.*, **55**, 2991 (1990).
7. C. Fehr, J.Galindo and S. Chappuis, *Tetrahedron Lett.*, **33**, 2465 (1992).
8. J. Mulzer and T. Kerkmann, *J. Am. Chem. Soc.*, **102**, 3620 (1980).

9. B. Linclau, P. De Clercq, M. Vandewalle, R. Bouillon and A. Verstuyf, *Bioorg. Med. Chem. Lett.*, **7**, 1465 (1997).

10. E. Vedejs, J. M. Dolphin and H. Mastalerz, *J. Am. Chem. Soc.*, **105**, 127 (1983).

11. M. Ishihara, T. Tsuneya, H. Shiota, M. Shiga and Y. Yokoyama, *Agric. Biol. Chem.*, **47**, 2121 (1983).

12. Y. Nishida, Y. Fukushima, H. Ohrui and H. Meguro, *ibid.*, **48**, 1217 (1984).

13. S. Hanessian, P. Murray and S. P. Sahoo, *Tetrahedron Lett.*, **26**, 5623 (1985).

14. D. Seebach and P. Renaud, *Helv. Chim. Acta*, **68**, 2342 (1985).

15. E. Nakamura, H. Oshino and I. Kuwajima, *J. Am. Chem. Soc.*, **108**, 3745 (1986).

16. Z. Jedlinski, M. Kowalczuk, P. Kurcok, M. Grzegorzek and J. Ermel, *J. Org. Chem.*, **52**, 4601 (1987).

17. M. Kowalczuk, P. Kurcok, W. Glowkowski and Z. Jedlinski, *ibid.*, **57**, 389 (1992).

18. D. Askin, R. P. Volante, R. A. Reamer, K. M. Ryan and I. Shinkai, *Tetrahedron Lett.*, **29**, 277 (1988).

19. L. A. Paquette, P. E. Wiedeman and P. C. Bulman-Page, *J. Org. Chem.*, **53**, 1441 (1988).

20. S. L. Schreiber, T. Sammakia and D. E Uehling, *ibid.*, **54**, 15 (1989).

21. M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling and S. L Schreiber, *J. Am. Chem. Soc.*, **112**, 5583 (1989).

22. K. Mori, K. Nomura, H. Kazuno and E. Yoshii, *Chem. Pharm. Bull. Jpn*, **38**, 1778 (1989).

23. M. E. Maier and B. Schoeffling, *Tetrahedron Lett.*, **32**, 53 (1991).

24. S. Hanessian, P. J. Roy, M. Petrini, P. J. Hodges, R. Di Fabio and G. Carganico, *J. Org. Chem.*, **55**, 5766 (1990).

25. C. Herdeis and K. Luetsch, *Tetrahedron: Asymmetry*, **4**, 121 (1993).

26. L. A. Paquette, A. M. Doherty and C. M Rayner, *J. Am. Chem. Soc.*, **114**, 3910 (1992).

27. A. Flores-Parra, D. M. Gutierrez-Avella, Y. J. Guzman-Vazquez, A. Ariza-Castolo and R. Contreras, *J. Org. Chem.*, **57**, 6067 (1992).

28. A. M. Diederich and D. M. Ryckman, *Tetrahedron Lett.*, **34**, 6169 (1993).

29. M. Sakurai, S. Higashida, M. Sugano, T. Nishi, F. Saito, Y. Ohata, H. Handa, T. Komi, R. Yogi,

T. Nishigaki and Y Yabe, *Chem. Pharm. Bull. Jpn*, **41**, 1378 (1993).

30. M. Sakurai, F. Saito, Y. Ohata, Y. Yabe and T. Nishi, *Chem. Commun.*, 1562 (**1992**).

31. T. Yamazaki, K. Mizutani and T. Kitazume, *J. Org. Chem.*, **58**, 4346 (1993).

32. K. Tomioka, Y.-S. Cho, F. Sato and K. Koga, *Chemistry Lett.*, 1621 (**1981**).

33. Y. Nishida, M. Konno, Y. Fukushima, H. Ohrui and H Meguro, *Agric. Biol. Chem.*, **50**, 191 (1986).

34. C. Anceau, G. Dauphin, G. Coudert and G. Guillaumet, *Bull. Soc. Chim. Fr.*, **131**, 291(1994).

35. H. Kigoshi, M. Ojika, T. Ishigaki, K. Suenaga, T. Mutou, A. Sakakura, T. Ogawa and K. Yamada, *J. Am. Chem. Soc.*, **116**, 7443 (1994).

36. N. Boudreault, R. G. Ball, C. Bayly, M. A. Bernstein and Y. Leblanc, *Tetrahedron*, **50**, 7947 (1994).

37. I. Giri, P. J. Bolon and C. K. Chu, *Nucleosides & Nucleotides*, **15**, 183 (1996).

38. M. E. Maier and S. Reuter, *Synlett*, 1029 (**1995**).

39. S. Takano, M. Yonaga, K. Chiba and K. Ogasawara, *Tetrahedron Lett.*, **21**, 3697 (1980).

40. S. Takano, N. Tamura and K Ogasawara, *Chem. Commun.*, 1155 (**1981**).

41. S. Takano, C. Kasahara and K. Ogasawara, *Chemistry Lett.*, 631 (**1982**).

42. S. Takano, M. Yonaga, M. Morimoto and K. Ogasawara, *J. Chem. Soc., Perkin Trans. 1*, 305 (**1985**).

43. (a) Y. Nishida, M. Konno, Y. Fukushima, H. Ohrui and H. Meguro, *Agric. Biol. Chem.*, **50**, 191 (1986). (b) C. H. Heathcock and S. J. Hecker, *J. Am. Chem. Soc.*, **108**, 4586 (1986).

44. A. H. Davidson, C. D. Floyd, A. J. Jones and P. L. Myers, *Chem. Commun.*, 1662 (**1985**).

45. M. Jalali, G. Boussac and J.-Y. Lallemand, *Tetrahedron Lett.*, **24**, 4307 (1983).

46. A. H. Fray, R. L. Kaye and E. F. Kleinman, *J. Org. Chem.*, **51**, 4828 (1986).

47. H. Bouchard, J. Soulie and J. Y. Lallemand, *Tetrahedron Lett.*, **32**, 5957 (1991).

48. J.-C. Harmange, B. Figadere and R. Hocquemiller, *Tetrahedron: Asymmetry*, **2**, 347 (1991).

49. T. B. Sells and V. Nair, *Tetrahedron*, **50**, 117 (1994).

50. J. V. N. V. Prasad and D. H. Rich, *Tetrahedron Lett.*, **31**, 1803 (1990).

51. C. Herdeis, K. Luetsch and D. Waibel, *Arch. Pharm.*, **280**, 41 (**1994**).

52. A. Dondoni, D. Perrone and M. T. Semola, *J. Org. Chem.*, **60**, 7927 (1995).

53. M. Menges and R. Brückner, *Liebigs Ann. Org. Biorg. Chem.*, **2**, 365 (1995).

54. E. Farrant and J. Mann, *J. Chem. Soc., Perkin Trans. 1*, 1083 (**1997**).

55. J. P. Robin, O. Gringore and E. Brown, *Tetrahedron Lett.*, **21**, 2709 (1980).

56. K. Tomioka, H. Mizuguchi and K. Koga, *Chem. Pharm. Bull. Jpn*, **30**, 4304 (1982).

57. A. Dondoni and D. Perrone, *Tetrahedron Lett.*, **33**, 7259 (1992).

58. A. K. Ghosh, S. P. McKee and W. J. Thompson, *J. Org. Chem.*, **56**, 6500 (1991).

59. S. Hormuth, H.-U. Reissig and D. Dorsch, *Angew. Chem., Int. Ed. Engl.*, **32**, 1449 (1993).

60. B. R. Lagu and D. C. Liotta, *Tetrahedron Lett.*, **35**, 547 (1994).

61. S. Hormuth and H. U. Reissig, *Angew. Chem., Int. Ed. Engl.*, **32**, 1449 (1993).

62. B. D. Dorsey, R. B. Levin, S. L. Mc Daniel, J. P. Vacca, J. P. Guare, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, J. C. Quintero, J. H. Lin, I.-W. Chen, M. K. Holloway, P. M. D. Fitzgerald, M. G. Axel, D. Ostovic, P. S. Anderson and J. R. Huff, *J. Med. Chem.*, **37**, 3443 (1994).

63. R. M. Keenan, D. F. Eppley and T. A. Tomaszek, *Tetrahedron Lett.*, **36**, 819 (1995).

64. A. Solladié-Cavallo, D. Roche, G. Bold, F. Acemoglu, M. Tintelnot-Blomley, J. Fischer, and A. Delian, *Tetrahedron: Asymmetry*, **7**, 1797 (1996).

65. H.-G. Capraro, G. Bold, A. Fässler, R. Cozens, T. Klimkait, J. Lazdins, J. Mestan, B. Poncioni, J. L. Rösel, D. Stover and M. Lang, *Arch. Pharm.*, **329**, 273 (1996).

66. K. Mori and S. Kuwahara, *Tetrahedron*, **42**, 5545 (1986).

67. Y. Fujimoto, Y. Ikuina, Y. Kanzawa, M. Nagakari, K. Kakimura and N. Ikekawa, *Heterocycles*, **30**, 275 (1990).

68. H. Kotsuki, H. Nishikawa, Y. Mori and M. Ochi, *J. Org. Chem.*, **57**, 5036 (1992).

69. P. A. Grieco and W. A. Carroll, *Tetrahedron Lett.*, **33**, 4401 (1992).

70. S. D. Burke, K. Shankaran and M. J. Helber, *ibid.*, **32**, 4655 (1991).

71. S. Kuwahara, Y. Shibata and A. Hiramatsu, *Ann.*, 993 (**1992**).

72. K. Tanaka, K. Ootake, K. Imai, N. Tanaka and A. Kaji, *Chemistry Lett.*, 633 (**1983**).

73. M. Asaoka, N. Fujii, K. Shima and H. Takei, *ibid.*, 805 (**1988**).

74. H. Yoda, H. Kitayama, T. Katagiri and K. Takabe, *Tetrahedron*, **48**, 3313 (1992).

75. P. A. Ganeshpure and R. Stevenson, *Australian J. Chem.*, **35**, 2175 (1982).

76. J.-P. Robin and Y. Landais, *J. Org. Chem.*, **53**, 224 (1988).

77. E. Brown and A. Daugan, *Tetrahedron*, **45**, 141 (1989).

78. K. Khamlach, R. Dhal and E. Brown, *ibid.*, **47**, 3787 (1990).

79. J.-P. Robin and Y. Landais, *ibid.*, **48**, 819 (1992).

80. K. Khamlach, R. Dhal and E. Brown, *Tetrahedron*, **48**, 10115 (1992).

81. T. Honda, N. Kimura, S. Sato, D. Kato and H. Tominaga, *J. Chem. Soc., Perkin Trans. 1.*, 1043 (**1994**).

82. T. Itoh, J.-i. Chika, Y. Takagi and S. Nishiyama, *J. Org. Chem.*, **58**, 5717 (1993).

83. D. Planchenault, R. Dhal and J.-P. Robin, *Tetrahedron*, **51**, 1395 (1995).

84. Y. Moritani, C. Fukushima, T. Ukita, T. Miyagishima, H. Ohmizu and T. Iwasaki, *J. Org. Chem.*, **61**, 6922 (1996).

85. J. W. Bode, M. P. Doyle, M. N. Protopopova and Q.-L. Zhou, *ibid.*, **61**, 9146 (1996).

86. E. Brown and A. Daugan, *Heterocycles*, **26**, 1169 (1987).

87. K. Tomioka, T. Ishiguro and K. Koga, *Tetrahedron Lett.*, **21**, 2973 (1980).

88. K. Tomioka, T. Ishiguro, Y. Iitaka and K. Koga, *Tetrahedron*, **40**, 1303 (1984).

89. J. P. Kutney, G. M. Hewitt, T. C. Jarvis, J. Palaty and S. J. Rettig, *Can. J. Chem.*, **70**, 2115 (1992).

90. S. Kawai, T. Hasegawa, M. Gotoh and H. Ohashi, *Phytochemistry*, **37**, 1699 (1994).

91. K. Lalami, R. Dhal and E. Brown, *Heterocycles*, **27**, 1131 (1988).

92. Y. Landais, J.-P. Robin and A. Leburn, *Tetrahedron*, **47**, 3787 (1991).

93. H. Shibuya, Y. Takeda, R.-s. Zhang, A. Tanitame, Y.-L. Tsai and I. Kitagawa, *Chem. Pharm. Bull. Jpn*, **40**, (1992).

94. P. Boissin, R. Dhal and E. Brown, *Tetrahedron*, **48**, 687 (1992).

95. Y. Nabi, R. Dhal and E. Brown, *Chemistry Lett.*, 1543 (**1983**).

96. E. Eich, H. Pertz, M. Kaloga, J. Schulz, M. R. Fesen, A. Mazumder and Y. Pommier, *J. Med. Chem.*, **39**, 86 (1996).

97. S. Danishefsky, R. L. Funk and J. F. Kerwin, *J. Am. Chem. Soc.*, **102**, 6889 (1980).

98. R. B. Miller and J. M. Frincke, *J. Org. Chem.*, **46**, 2972 (1981).

99. P. A. Bartlett and C. F. Pizzo, *ibid.*, **46**, 3896 (1981).

100. P. A. Grieco and C. V. Srinivasan, *ibid.*, **46**, 2591 (1981).

101. Y. Inouye, C. Fukuya and H. Kakisawa, *Bull. Chem. Soc. Jpn*, **54**, 1117 (1981).

102. C. R. Noe, *Chem. Ber.*, **115**, 1591 (1982).

103. W.-S. Zhou and W.-S. Tian, *Tetrahedron*, **43**, 3705 (1987).

104. M. Kahn and B. Chen, *Tetrahedron Lett.*, **28**, 1623 (1987).

105. S. Hanessian and P. J. Murray, *J. Org. Chem.*, **52**, 1170 (1987).

106. D. Friedrich and F. Bohlmann, *Tetrahedron*, **44**,1369 (1988).

107. T. Wakamatsu, N. Miyachi, F. Ozaki, M. Shibasaki and Y. Ban, *Tetrahedron Lett.*, **29**, 3829 (1988).

108. M. Dischmann, L. Ernst and H. Wolf, *Ann.*, 727 (**1989**).

109. A. J. Carnell, S. M. Roberts, V. Sik and A. J. Willetts, *Chem. Commun.*, 1438 (**1990**).

110. A. J. Carnell, S. M. Roberts, V. Sik and A. J. Willetts, *J. Chem. Soc., Perkin Trans. 1*, (**1991**).

111. D. P. Richardson, T. E. Smith, W. W. Lin, C. N. Kiser and B. R. Mahon, *Tetrahedron Lett.*, **31**, 5973 (1990).

112. C.-y. Chen and D. J Hart, *J. Org. Chem.*, **55**, 6236 (1990).

113. C.-y. Chen and D. J. Hart, *ibid.*, **58**, 3840 (1993).

114. A. Rashid, G. M. Taylor, W. W. Wood and D. Alker, *J. Chem. Soc., Perkin Trans. 1*, 1289 (**1990**).

115. F. E. Ziegler and J. S. Tung, *J. Org. Chem.*, **56**, 6530 (1991).

116. D. Alker, D. N. Jones, G. M. Taylor and W. W. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1119 (**1992**).

117. M. Carda andJ. A. Marco, *Tetrahedron*, **48**, 9789 (1992).

118. M. Tada, H. Yamada, A. Kanamori and K. Chiba, *J. Chem. Soc., Perkin Trans. 1*, 239 (**1993**).

119. M. F. Semmelhack, W. R. Epa, A. W.-H. Cheung, Y. Gu, C. Kim, N. Zhang and W. Lew, *J. Am. Chem. Soc.*, **116**, 7455 (1994).

120. J. C. Mc Williams and J. Clardy, *ibid.*, **116**, 8378 (1994).

121. P. Wipf, Y. Kim and D. M. Goldstein, *ibid.*, **117**, 11106 (1995).

122. Y. Morimoto, M. Iwahashi, K. Nishida, Y. Hayashi and H. Shirahama, *Angew. Chem., Int. Ed. Engl.*, **35**, 981 (1996).

123. K. M. Davis and B. K. Carpenter, *J. Org. Chem.*, **61**, 4617 (1996).

124. A. A. Devreese, P. J. De Clercq and M. Vandewalle, *Tetrahedron Lett.*, 4767 (**1980**).

125. A. A. Devreese, M. Demuynck, P. J. De Clercq and M. Vandewalle, *Tetrahedron*, **39**, 3049 (1983).

126. W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **45**, 4111 (1980).

127. M. Kocor, M. M. Kabat, J. Wicha and W. Peczynska-Czoch, *Steroids*, **41**, 55 (1983).

128. J. Mulzer, N. Salimi and H. Hartl, *Tetrahedron: Asymmetry*, **4**, 457 (1993).

129. G. Casiraghi, L. Pinna, G. Rassu, P. Spanu and F. Ulgheri, *ibid.*, **4**, 681 (1993).

130. U. Nubbemeyer, *Synthesis*, 1120 (**1993**).

131. H. Takahata, Y. Uchida and T. Momose, *J. Org. Chem.*, **60**, 5628 (1995).

132. D. F. Taber and Y Song, *ibid.*, **61**, 7508 (1996).

133. D. F. Taber and Y Song, *ibid.*, **61**, 7508 (1996).

134. K. Suzuki, T. Tatsuoka, T. Ishihara, T. Ohno, K. Aisaka, R. Ogino, M. Kuroki, F. Satoh, S. Miyano and K. Sumoto, *Chem. Pharm. Bull. Jpn*, **44**, 132 (1996).

135. F. Kido, Y. Noda and A. Yoshikoshi, *Chem. Commun.*, 1209 (**1982**).

136. A. B. Smith and R. E. Richmond, *J. Am. Chem. Soc.*, **105**, 575 (1983).

137. F. Kido, Y. Noda and A. Yoshikoshi, *Tetrahedron*, **43**, 5467 (1987).

138. S. Hatakeyama, K. Saijo and S. Takano, *Tetrahedron Lett.*, **26**, 865 (1985).

139. E. B. Villhauer and R. C. Anderson, *J. Org. Chem.*, **52**, 1186 (1987).

140. P. Kocienski, K. Jarowicki and S. Marczak, *Synthesis*, 1191 (**1991**).

141. K. Iguchi, M. Kitade, Y. Yamada, A. Ichikawa, I. Ohtani, T. Kusumi and H. Kakisawa, *Chemistry Lett.*, 319 (**1991**).

142. I. Yamamoto and K Narasaka, *Bull. Chem. Soc. Jpn*, **67**, 3327 (1994).

143. H.-E. Radunz, V. Eiermann, G. Schneider and A. Riethmueller, *Tetrahedron*, **47**, 1887 (1991).

144. L. A. Paquette, S. Hormuth and C. J. Lovely, *J. Org. Chem.*, **60**, 4813 (1995).

145. F. Sanchez-Sancho, S. Valverde and B. Herradon, *Tetrahedron: Asymmetry*, **7**, 3209 (1996).

146. S. Takano, K. Inomata, A. Kurotaki, T. Ohkawa and K. Ogasawara, *Chem. Commun.*, 172 (**1987**).

147. J. Corbera, J. Font, M. Monsalvatje, R. M. Ortuno and F. Sanchez-Ferrando, *J. Org. Chem.*, **53**, 4393 (1988).

148. F. E. Ziegler and H. Kim, *Tetrahedron Lett.*, **34**, 7669 (1993).

149. K. F. Cheng, T. T. Wong, K. P. and Y. C Chan, Kong, *Eur. J. Med. Chem. Chim. Ther.*, **27**, 121 (1992).

150. Y. Moritani, C. Fukushima, T. Ogiku, T. Ukita, T. Miyagishima and T. Iwasaki, *Tetrahedron Lett.*, **34**, 2787 (1993).

151. Y. Moritani, C. Fukushima, T. Ukita, T. Miyagishima, H. Ohmizu and T. Iwasaki, *ibid.*, **61**, 6922 (1996).

152. H. Pellissier, P. Y. Michellys and M. Santelli, *J. Org. Chem.*, **62**, 5588 (1997).

153. A. G. Schultz and J. D Godfrey, *J. Am. Chem. Soc.*, **102**, 2414 (1980).

154. E. J. Corey and M.-C. Kang, *ibid.*, **106**, 5384 (1984).

155. E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, **26**, 4291 (1985).

156. R. K. Boeckman, D. K. Heckendorn and R. L. Chinn, *ibid.*, **28**, 3551 (1987).

157. R. K. Boeckman, S. K. Yoon and D. K. Heckendorn, *J. Am. Chem. Soc.*, **113**, 9682 (1991).

158. T. J. Sprules and J.-F. Lavallée, *J. Org. Chem.*, **60**, 5041 (1995).

159. S. M. Adekenov and N. M. Gafurov, *Chem. Nat. Compds (Engl. Transl.)*, **28**, 452 (1992).

160. M. Bukowska and J. Prejzner, *Pol. J. Chem.*, **68**, 699 (1994).

161. G. A. Molander and C. R. Harris, *J. Am. Chem. Soc.*, **117**, 3705 (1995).

162. S. C. Welch, A. S. C. P. Rao, C. G. Gibbs and R. Y. Wong, *J. Org. Chem.*, **45**, 4077 (1980).

163. J. Ishihara, R. Nonaka, Y. Terasawa, K.-i. Tadano and S Ogawa, *Tetrahedron: Asymmetry*, **5**, 2217 (1994).

164. T. Hudlicky, F. Koszyk, D. M. Dochwat and G. L. Cantrell, *J. Org. Chem.*, **46**, 2911 (1981).

165. F.-T. Hong and L. A. Paquette, *Tetrahedron Lett.*, **35**, 9153 (1994).

166. K. Matsuo and T. Arase, *Chem. Pharm. Bull. Jpn*, **43**, 2091 (1995).

167. R. Zinuck, N. J. Liverton and A. B. Smith, *J. Am. Chem. Soc.*, **108**, 2451 (1986).

168. J. D. White, T. C. Somers, G. N. Reddy, *ibid.*, **108**, 5352 (1986).

169. S. V. Ley, J. Norman and C. Pinel, *Tetrahedron Lett.*, **35**, 2095 (1994).

170. M. Nishizawa, H. Yamada, Y. Yamaguchi, S. Hatakeyama and I.-S. Lee, *Chemistry Lett.*, **8**, 1555 (1994).

171. H. Yamada and M. Nishizawa, *J. Org. Chem.*, **60**, 386 (1995).

172. V. K. Yadav and K. K. Kapoor, *Tetrahedron*, **51**, 8573 (1995).

173. Y. Sakito, S. Tanaka, M. Asami and T. Mukaiyama, *Chemistry Lett.*, 1223 (**1980**).

174. M. K. Kaloustian and F. Khouri, *J. Am. Chem. Soc.*, **102**, 7579 (1980).

175. U. Sunay and B. Fraser-Reid, *Tetrahedron Lett.*, **27**, 5335 (1986).

176. T.-F. Wang and C.-F. Yang, *Chem. Commun.*, 1876 (**1989**).

177. J. M. Takacs and Y. C. Myoung, *Tetrahedron Lett.*, **33**, 317 (1992).

178. D. Tanaka, T. Yoshino, I. Kouno, M. Miyashita and H Irie, *Tetrahedron*, **49**, 10253 (1993).

179. S. Takano, M. Morimoto, K. Masuda and K. Ogasawara, *Chem. Pharm. Bull. Jpn*, **30**, 4238 (1982).

180. S. Takano, K. Masuda, S. Hatakeyama and K. Ogasawara, *Heterocycles*, **19**, 1407 (1982).

181. S. Takano, S. Hatakeyama, Y. Takahashi and K. Ogasawara, *ibid.*, **17**, 263 (1982).

182. D. J. Burnell and Y.-J. Wu, *Can. J. Chem.*, **68**, 804 (1990).

183. H. Iwadate, K. Gamoh, Y. Fujimoto and N. Ikekawa, *Chem. Pharm. Bull. Jpn*, **34**, 2061 (1986).

184. T. Kametani, M. Tsubuki and T. Honda, *Heterocycles*, **28**, 59 (1989).

185. D. L. J. Clive, K. S. K. Murthy, A. G. H.; Wee, J. S. Prasad and G. V. J. Silva, *J. Am. Chem. Soc.*, **112**, 3018 (1990).

186. S. E. Mac Whorter and N. E. Schore, *J. Org. Chem.*, **56**, 338 (1991).

187. M. Kawamura and K. Ogasawara, *Tetrahedron Lett.*, **36**, 3369 (1995).

188. P. A. Grieco, E. Williams, H. Tanaka and S. Gilman, *J. Org. Chem.*, **45**, 3537 (1980).

189. D. J. Morgans, *Tetrahedron Lett.*, **22**, 3721 (1981).

190. W. A. Kinney, M. J. Coghlan and L. A. Paquette, *J. Am. Chem. Soc.*, **107**, 7352 (1985).

191. Y. Kobayashi, Y. Kitano, Y. Takeda and F. Sato, *Tetrahedron*, **42**, 2937 (1986).

192. S. Hacini and M. Santelli, *ibid.*, **46**, 7787 (1990).

193. H. Akita, H. Yamada, H. Matsukura, T. Nakata and T. Oishi, *Tetrahedron Lett.*, **31**, (1990).

194. M. Miyashita, Y. Toshimitsu, T. Shiratani and H. Irie, *Tetrahedron: Asymmetry*, **4**, 1573 (1993).

195. P. A. Grieco, J. Inanaga, N.-H. Lin and T. Yanami, *J. Am. Chem. Soc.*, **104**, 5781 (1982).

196. J. R. Rocca, J. H. Tumlinson, B. M. Glancey and C. S. Lofgren, *Tetrahedron Lett.*, **24**, 1893 (1983).

197. S. Tanimori and M. Nakayama, *Agric. Biol. Chem.*, **54**, 775 (1990).

198. P. G. M. Wuts, M. L. Obrzut and P. A Thompson, *Tetrahedron Lett.*, **25**, 4051 (1984).

199. P. G. M. Wuts and S. S. Bigelow, *J. Org. Chem.*, **53**, 5023 (1988).

200. N. Ouvrard, J. Rodriguez and M. Santelli, *Tetrahedron Lett.*, **34**, 1149 (1993).

201. W. Pinyarat and K. Mori, *Biosci. Biotechnol. Biochem.*, **57**, 419 (1993).

202. T. Honda, H. Ishizone, K. Naito and Y. Suzuki, *Heterocycles*, **31**, 1225 (1990).

203. D. Friedrich and L. A. Paquette, *J. Org. Chem.*, **56**, 3831 (1991).

204. A. J. Caruso, J. Polonsky and B. S. Rodriguez, *Tetrahedron Lett.*, **25**, 2567 (1982).

205. H. Nagaoka, K. Kobayashi, T. Matsui and Y. Yamada, *ibid.*, **28**, 2021 (1987).

206. H. Nagaoka, K. Kobayashi and Y. Yamada, *ibid.*, **29**, 5945 (1988).

207. J. Wagner and P. Vogel, *Chem. Commun.*, 1634 (**1989**).

208. J. Wagner and P. Vogel, *Tetrahedron Lett.*, **32**, 3169 (1991).

209. A. R. Daniewski and T. Warchol, *Ann.* 965 (**1991**).

210. I. Fleming and S. K. Ghosh, *Chem. Commun.*, 2285 (**1994**).

211. F. W. J. Demnitz and R. A. Raphael, *Synthesis*, 1305 (**1996**).

(Received May 12, 1999; in final form September 13, 1999)