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Organocatalytic Michael addition, a convenient tool in total synthesis. First asymmetric synthesis of (−)-botryodiplodin

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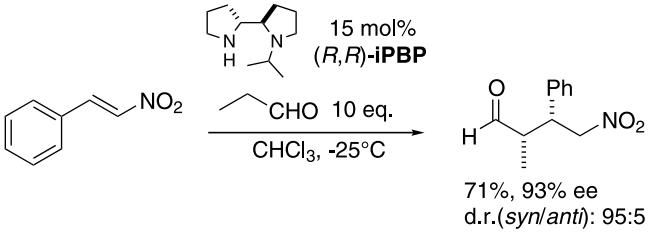
Abstract—The asymmetric Michael addition of propionaldehyde to (2*E*)-(3-nitro-but-2-enyloxymethyl)-benzene **8**, catalyzed by the chiral diamine (*S*,*S*)-*N*-*i*Pr-2,2′-bipyrrolidine, afforded, with 93% ee, a precursor **9** of (−)-botryodiplodin. The nitro functionality of **9** was converted to a ketone via a Nef reaction to give, after a few steps, the enantiomerically enriched (−)-botryodiplodin.

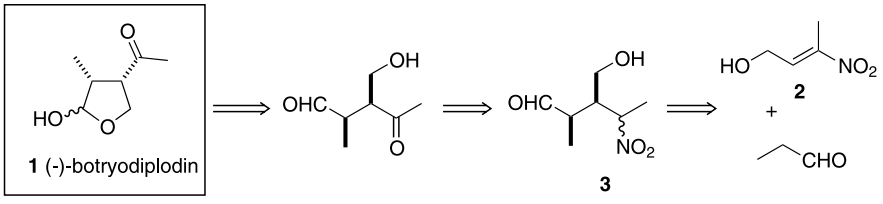
Recently, Barbas et al.[1] described the first asymmetric addition of aldehydes and ketones to nitrostyrene catalyzed by diamines or L-proline. List[2] and Enders[3] have also reported the asymmetric addition of ketones to nitrostyrene catalyzed by L-proline. For our part, we have developed new *N*-substituted derivatives of 2,2′-bipyrrolidine (Scheme 1) as organocatalysts for the asymmetric Michael addition to nitroolefins.[4] The best result was obtained for the addition of propionaldehyde catalyzed by (*R*,*R*)-*N*-*i*Pr-2,2′-bipyrrolidine ((*R*,*R*)-**iPBP**) which gave the addition product with 93% ee[5] and a diastereomeric ratio (*syn*/*anti*) of 95:5.



Scheme 1. Asymmetric addition of propionaldehyde to nitrostyrene catalyzed by chiral (*R*,*R*)-***i*PBP**.

The high enantiocontrol and *syn* diastereocontrol of this Michael addition led us to consider its application towards the synthesis of (−)-botryodiplodin **1**.[6] In 1966, Sen Gupta et al.[7] isolated this antibiotic from *Botryodiplodia theobromae* after which Arsenault[8] confirmed its structure. Furthermore, (−)-botryodiplodin was discovered as a secondary metabolite of *Penicillium roqueforti*.[9] This mycotoxin exhibits antibiotic and antileukemic activity[10] but is also a mutagen[11] and induces linkage between proteins and DNA.[12,13] To date, only two syntheses of this natural product in enantiomerically pure form have been described,[14,15] both of them using chiral building blocks derived from natural products (D-ribose and methylenomycin A).

A retrosynthetic analysis of (−)-botryodiplodin (Scheme 2) leads to nitro compound **3**, which is a direct precursor of the open form of **1**. Indeed, the nitro group can



Scheme 2. Retrosynthetic analysis for (−)-botryodiplodin.

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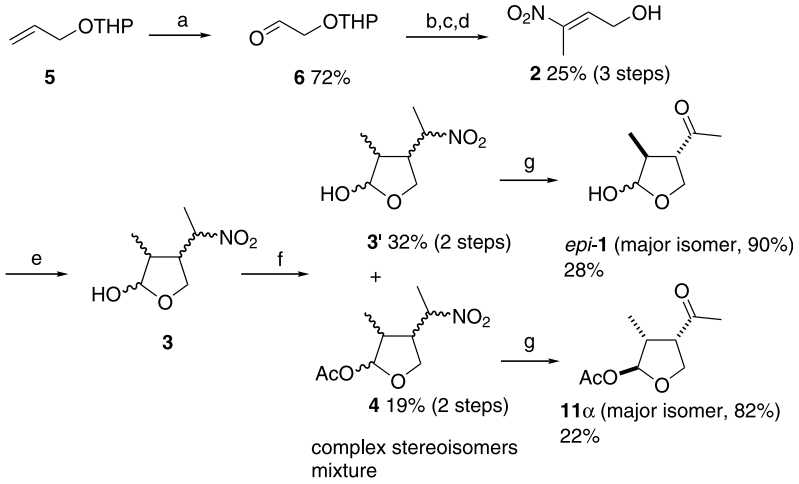
be readily transformed to a carbonyl group via the Nef reaction.[16] The nitro compound **3** may arise from a Michael addition of propionaldehyde to the nitroolefin **2**. This last step could be catalyzed by our chiral diamine (*S*,*S*)-**iPBP** to provide the adduct **3** in an enantiomerically enriched form.

We started with the preparation of the nitroolefin **2** (Scheme 3), which was readily obtained from the THP-protected allyl alcohol **5**. Aldehyde **6** was prepared by ozonolysis of **5** and then nitroolefin **2** was obtained via Henry condensation[17] followed by deprotection of the alcohol. The key step of our synthesis was the organocatalyzed addition of propionaldehyde to the nitroolefin **2**. Preliminary investigations on a racemic version, were done using pyrrolidine instead of (*S*,*S*)-**iPBP**. The first results immediately showed the difficulties of our approach. Indeed, the addition led to the simultaneous formation of four stereocentres. Unfortunately, these centres were not well controlled, providing a very complex mixture of diastereomers **3**, from which no major isomer could be distinguished. Acetylation of the crude mixture led to the isolation of compounds **4** in low yield, along with an equivalent amount of starting material **3′**. After separation, the nitro functionality of both **3′** and **4** was converted to a carbonyl group using conditions described by Wade.[18] Surprisingly, reaction of **4** led predominantly to the product **11**, and compound **3′** to the product *epi*-**1**, indicating that the previous acetylation had occurred more efficiently on the 3,4-*cis* diastereomer. This direct approach allowed us to obtain (−)-botryodiplodin but the yields were low and it was difficult to analyze clearly each intermediate or to separate the diastereomers. These considerations forced us to reconsider our strategy toward the synthesis of (−)-botryodiplodin.

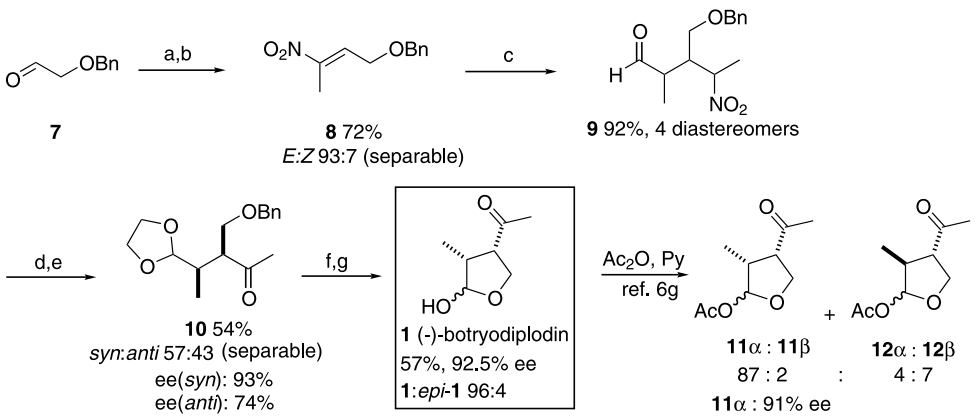
To avoid the direct formation of the lactol form of (−)-botryodiplodin, the hydroxy group of the nitroolefin **2** was protected with a benzyl group. Nitroolefin **8** was obtained in two steps via a Henry condensation starting from the commercially available benzyloxacetaldehyde **7** in 72% yield for the two steps (Scheme 4). The asymmetric Michael addition of propionaldehyde to nitroolefin **8** was performed with the chiral (*S*,*S*)-**iPBP** diamine. The adduct **9** was isolated as a mixture of four diastereomers in 92% yield after seven days at −10°C. At this stage we were not able to measure the enantiomeric excess or to separate the diastereomers.

We then tested several conditions to transform the nitro group to the corresponding ketone,[19] but all led either to the decomposition or to the recovery of the starting material, probably due to the high instability of the desired 1,4-ketoaldehyde. This was confirmed after protection of the aldehyde as the corresponding 1,3-dioxolane, which then allowed the transformation of the nitro group to the ketone without decomposition. This transformation was performed using the mild conditions developed by Wade[18] with sodium nitrite and isoamyl nitrite in DMSO. After four days at room temperature the nitro group had totally disappeared to give the ketone **10** in 54% yield. In this reaction a stereocentre was removed and allowed the measurement of the enantiomeric excess of each diastereomer by chiral supercritical fluid chromatography (SFC).[20] The diastereomeric ratio, *syn*/*anti* was 57:43 and the enantiomeric excesses were 93% for the *syn* adduct and 74% for the *anti* adduct. As predicted the enantiomeric excess of the *syn* compound was relatively high but the diastereocontrol was almost nonexistent. We cannot, presently, explain this lack of diastereocontrol compared to the addition to nitrostyrene.[4] Fortunately, the two diastereomers were separable by flash chromatography on silica gel.

The end of the synthesis consists of only two deprotection steps, the first one being a H_2/Pd/C debenzylation



Scheme 3. Direct approach towards (±)-botryodiplodin. *Reagents and conditions*: (a) i O_3, CH_2Cl_2, −78°C. ii Me_2S, −78°C to +20°C, 15 h, 65%; (b) 1,1,3,3-tetramethylguanidine 15 mol%, $EtNO_2$, THF, 0°C, 3 h, 90%; (c) TFAA, Et_3N, −10°C, 1 h, 47%; (d) TsOH 10 mol%, MeOH, rt, 1 h, 85%; (e) propionaldehyde 10 equiv., pyrrolidine 15 mol%, $CHCl_3$, 1 d, rt, not isolated; (f) Ac_2O, Py, rt, 15 h, **4** 19%+**3′** 32%; (g) isoamyl nitrite, $NaNO_2$, DMSO, 4 d, rt.



Scheme 4. *Reagents and conditions*: (a) $EtNO_2$, 1,1,3,3-tetramethylguanidine 15 mol%, THF, 0°C, 3 h, quant.; (b) TFAA, Et_3N, −10°C, 1 h, 72%; (c) propionaldehyde 10 equiv., (*S*,*S*)-*i*PBP 15%, $CHCl_3$, −10°C, 7 d, 92%; (d) ethylene glycol, PPTS 10 mol%, C_6H_6, Dean–Stark, 3 h, 74%; (e) $NaNO_2$, isoamyl nitrite, DMSO, rt, 4 d, 73%; (f) $Pd(OH)_2/C$ 15%, H_2 1 atm, MeOH, rt, 3 h, 91%; (g) HCl 10^{-2} M, ether, rt, 3 d, 62%.

to provide the crude free alcohol in 91% yield. Attempts to purify the alcohol led only to a complex mixture of the desired product, a partially hydrolyzed product and a new compound resulting from an intramolecular transacetalization. For this reason the crude was used without further purification for the next step. The second deprotection was carried out in a biphasic mixture of dilute aqueous hydrochloric acid (10^{-2} M solution) and ether, and vigorously stirred for three days at room temperature to give (−)-botryodiplodin in 62% yield after filtration through silica gel. Use of a more acidic solution increased the reaction rate but damaged a large part of product via β-elimination to the corresponding α,β-unsaturated ketone.

The purity of (−)-botryodiplodin was determined by chiral GC;[21] the enantiomeric excess was 92.5%, and only 4% of the *anti* product (*epi*-botryodiplodin *epi*-**1**) was detected. Optical rotation measurements confirmed the negative sign of the isolated product: $[\alpha]_D^{25} = -62.5$ (*c* 2.5, 92.5% ee, $CHCl_3$); lit.[15] $[\alpha]_D^{25} = -69$ (*c* 1, $CHCl_3$).

The structure of (−)-botryodiplodin was unambiguously assigned after acetylation and comparison of the ^1H and ^{13}C NMR spectra of acetate **11** with literature data.[6g] Chiral GC was used to separate the mixture of eight acetylated products.[22] The enantiomeric excess of **11**α was still 91% but the diastereomeric ratio between **11** and **12** had slightly decreased due to the basic media employed during the formation of the acetylated derivative.

In conclusion, we have described a short and highly enantioselective synthesis of (−)-botryodiplodin **1** and have demonstrated the potential of organocatalysis in asymmetric total synthesis. Moreover, our synthesis could be applied to the synthesis of a large variety of analogues by simply changing the starting nitroalkane or aldehyde.

Acknowledgements

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References

1. (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260; (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 4441; (c) Betancort, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737.
2. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
3. Enders, D.; Seki, A. *Synlett* **2002**, 26.
4. (a) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611; (b) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.
5. New experiments have revealed a problem with the optical purity of some crops of our chiral diamine, which was only 89% ee. With an optically pure diamine **iPBP**, under the same conditions, we have now obtained the adduct with 93% ee and 95:5 dr instead of 83% ee and 95:5 dr (Ref. 4a).
6. For other syntheses of racemic botryodiplodin see: (a) McMurry, P. M. J.; Abe, K. *J. Am. Chem. Soc.* **1973**, *95*, 5824; (b) McMurry, P. M. J.; Abe, K. *Tetrahedron Lett.* **1973**, *14*, 4103; (c) Mukaiyama, T.; Wada, M.; Hanna, J. *Chem. Lett.* **1974**, *94*, 1181; (d) Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309; (e) Kurth, M. J.; Yu, C.-M. *J. Org. Chem.* **1985**, *50*, 1840. (f) Dulcere, J. P.; Mihoubi, M. N.; Rodriguez, J. *J. Org. Chem.* **1993**, *58*, 5709; (g) Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976; (h) Nouguier, R.; Gastaldi, S.; Stien, D.; Bertrand, M.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3371; (i) Villar, F.; Andrey, O.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3375.

7. Gupta, R. S.; Chandran, R. R.; Diverkar, P. V. *Ind. J. Exp. Biol.* **1966**, *4*, 152.
8. Arsenault, G. P.; Althaus, J. R.; Divekar, P. V. *J. Chem. Soc., Chem. Commun.* **1969**, 1414.
9. Moreau, S.; Lablache-Combier, A.; Biguet, J.; Foulon, C.; Delfosse, M. *J. Org. Chem.* **1982**, *47*, 2358.
10. Renauld, F.; Moreau, S.; Lablache-Combier, A. *Tetrahedron* **1984**, *40*, 1823.
11. Moulé, Y.; Decloitre, F.; Hamon, G. *Envir. Mut.* **1981**, *3*, 287.
12. Moulé, Y.; Renauld, F.; Darracq, N.; Douce, C. *Carcinogenesis* **1982**, *3*, 211.
13. Douce, C.; Moreau, S.; Decloitre, F.; Moulé, Y. *Carcinogenesis* **1982**, *3*, 587.
14. Sakai, K.; Amemiya, S.; Inoue, K.; Kojima, K. *Tetrahedron Lett.* **1979**, *20*, 2364.
15. Rehnberg, N.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 3589.
16. (a) Pinnick, H. W. *Org. React. (N.Y.)* **1990**, *38*, 655; (b) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 263.
17. (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds. The Henry (nitroaldol) Reaction; Pergamon Press: Oxford, 1991; Vol. 2, pp. 321–340; (b) Ono, N. In *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (c) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751; (d) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.
18. Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418.
19. (a) MeOLi, O_3, Me_2S: McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259; (b) Et_3N, CAN: Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44; (c) TPAP, NMO, AgOAc, K_2CO_3, MS: Tokunaga, Y.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 207; (d) MeOLi, conc. H_2SO_4, HCl 1N: Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716; (e) $TiCl_3$, NH_4OAc: McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.
20. The racemic compound was previously formed with pyrrolidine as catalyst for the Michael addition. Separation of the enantiomers: SFC, Daicel CHIRALCEL OJ column, 1% MeOH, R_t (**10**-s*yn*): 4.6, 6.4 min, R_t (**10**-*anti*): 5.2, 5.6 min.
21. Hydrodex-B-3P, 60°C–1°C/min–100°C–10°C/min–170°C–10 min, R_t (**1**α): 48.7, 48.9 min, R_t (**1**β): 48.2 min.
22. Hydrodex-B-3P, 80°C–1°C/min–170°C, R_t (**11**α): 36.7, (–)-isomer 38.4 min, R_t (**11**β): 35.2, 36.3 min, R_t (**12**α): 34.2, 34.8 min, R_t (**12**β): 38.7, 39.3 min.