Pergamon

Tetrahedron Letters, Vol. 37, No. 20, pp. 3501-3504, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00563-1

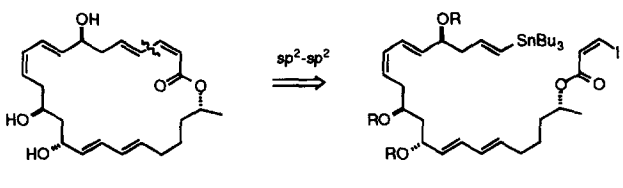
Sequential sp^2-sp^2 Coupling Reactions in Polyene Macrolide Synthesis. A Novel Approach to Macrolactin A

Richard J Boyce and Gerald Pattenden*

Department of Chemistry, Nottingham University, Nottingham NG7 2RD, England

Abstract: A combination of two intermolecular sp^2-sp^2 (Stille and Suzuki) coupling reactions, is employed to elaborate the precursor **2**, used in an intramolecular Stille sp^2-sp^2 macrocyclisation leading to the hexaene macrolide system **1** found in the macrolactin family of bio-active marine metabolites.

The macrolactins are a novel and unusual family of polyene macrolides which have recently been isolated from a taxonomically undefined deep sea marine bacterium.[1] The parent aglycone, macrolactin A **1**, shows a structure based on a 24-membered macrolide incorporating three stereodefined (*Z,E*-; *E,Z*-; *E,E*-) 1,3-diene units separated by four chiral secondary hydroxy/oxy centres. Macrolactin A is an extremely cytotoxic compound which has been shown to inhibit B16-F10 murine melanoma cancer cells and mammalian *Herpes simplex* viruses, and to protect T-lymphoblast cells against human HIV viral replication. The novel structure and interesting biological profile shown by macrolactin A have combined to make the compound an interesting synthetic target.[2] We now describe a total synthesis of the macrolactin structure which features the judicious use of sp^2-sp^2 coupling reactions[3] to elaborate all three stereodefined 1,3-diene units in the compound, including a final Stille macrocyclisation.

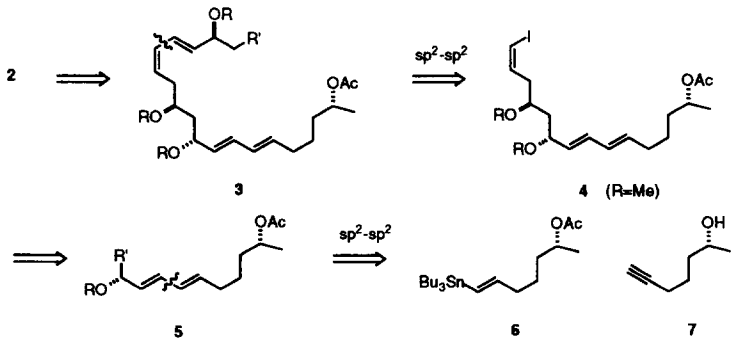


1 **2**

Scheme 1

The strategy we have followed to macrolactin A was based on the Stille sp^2-sp^2 macrocyclisation reaction shown in Scheme 1, as a key step. This stratagem, which we have used earlier in an approach towards the antitumoral antibiotic substance leinamycin,[4] has recently become a feature of several synthetic approaches to macrocyclic natural products.[5,6] In turn, we also elected to synthesise the acylic precursor **2** sequentially from the tetraene **3** and the diene **5**, where the stereodefined 1,3-diene units in these precursors were elaborated similarly by sp^2-sp^2 coupling reactions involving vinylmetallic and vinyl halide partners (Scheme 2).

Thus, we first synthesised the *E,E* 1,3-diene **12** containing three of the chiral centres in macrolactin A, using a Stille coupling reaction between the vinylstannane **6** and the vinyl iodide **11**. The vinylstannane **6** was



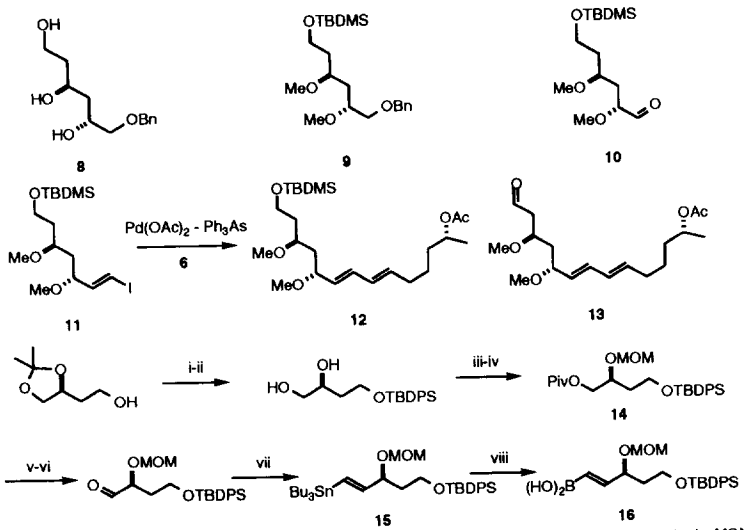
Scheme 2

smoothly prepared from the known chiral alcohol **7**[7], following hydrostannation (Bu_3SnH, AIBN, 80°C; 90%) and acetylation (Ac_2O, Et_3N, DMAP; 88%),[8] whereas the vinyl iodide **11** was produced from the triol **8**[9] *via* the *bis*-methyl ether **9** (TBDMSCl, DMAP, Et_3N, CH_2Cl_2; 94%: then NaH, MeI, THF; 89%), the aldehyde **10** (Na, NH_3, glyme; 84%, then DMSO, $pySO_3$, Et_3N; 68%), and a Takai reaction[10] (CHI_3, $CrCl_2$, THF; 65%) with **10**. Treatment of a mixture of **11** and **6** with a solution of $Pd(OAc)_2$ - Ph_3As[11] in DMF (RT, 8h) then resulted in smooth Stille coupling to produce the *E,E*-diene **12** as a colourless oil in 94% yield.[8]

In readiness for the second sp^2-sp^2 coupling reaction, the 1,3-diene **12** was now elaborated to the *Z*-vinyl iodide **4** following: i, deprotection to the corresponding primary alcohol (TBAF, THF, 82%), ii, oxidation to the aldehyde **13** (Dess-Martin periodinane; 82%); and iii, a Wittig reaction [$I^-Ph_3\ P^+\ CH_2\ I$, $NaN(TMS)_2$, HMPA, THF; 53%]. The C_7 *E*-vinylstannane **15** was obtained from the known protected triol **14**[12] produced from L-malic acid, according to the details shown in Scheme 3. Several attempts were then made to couple the vinylstannane **15** with the vinyl iodide **4** under a variety of reaction conditions in the presence of different palladium catalysts. Unfortunately, under all conditions, a mixture of new *Z,E*- and *E,E*- 1,3-dienes was always obtained, in low yields, and only after extended reaction times. This observation is consistent with observations made earlier by Stille *et al*[13] in other coupling reactions involving *Z*-vinyl iodides. We then decided to carry out the aforementioned coupling reaction to the tetraene **17** using a Suzuki reaction[14] with the boronic acid **16** corresponding to **15**. Thus, the vinylboronic acid **16** was smoothly produced from the vinylstannane **15** following tin- lithium transmetallation using butylithium and treatment with trimethylborate (62% overall). To our pleasure when the vinyl iodide **4** and the vinyl boronic acid **16** were treated with palladium tetrakis(triphenylphosphine) in the presence of thallium hydroxide,[15] the required newly formed *Z,E*- 1,3-diene **17** was isolated in 78% yield as a single isomer.

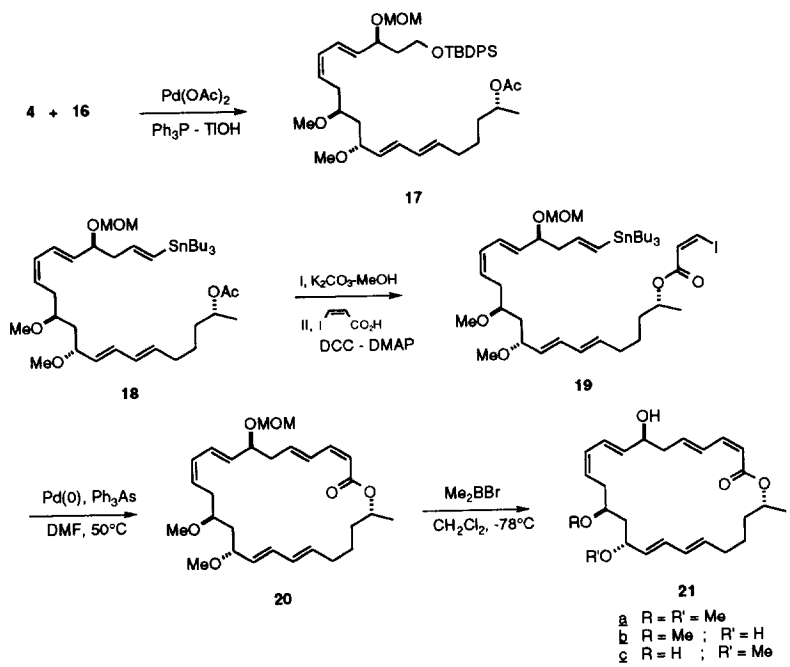
Deprotection of the silyl ether group in **17** (TBAF, THF, 81%), followed by oxidation of the resulting alcohol (Dess-Martin periodinane; 89%), and a Takai reaction ($Bu_3SnCHBr_2$, $Cr\ Cl_2$, LiI, DMF, THF; 28%)[16] next led to the vinyl stannane **18** as a colourless oil. The synthesis of the key intermediate **19** was now completed following saponification of the ester group in **18** to the corresponding alcohol ($K_2\ CO_3$, MeOH; 80%), and condensation with *Z*-iodoacrylic acid[17] (DCC, DMAP, -20°C; 80%).

When the vinyl stannane-vinyl iodide **19** was treated with Ph_3As - palladium(O) dibenzylideneacetone dimer (dry DMF, 60°C, 1h) it underwent smooth intramolecular Stille coupling to produce the macrocycle **20** in an



Reagents: i, TBDPS-Cl, Et_3N, DMAP, CH_2Cl_2, 98%; ii, $HS(CH_2)_2SH$, pTSA, $CHCl_3$, Δ, 60%; iii, Piv-Cl, Et_3N, CH_2Cl_2, 93%; iv, MOM-Cl, DIPEA, $CHCl_3$, Δ, 80%; v, DIBAL-H, CH_2Cl_2, -78°C, 95%; vi, $Py.SO_3$, DMSO, Et_3N, 83%; vii, $Bu_3SnCHBr_2$, $CrCl_2$, LiI, THF, DMF, 54%; viii, ^nBuLi, $B(OMe)_3$, THF, -78°C, 62%

Scheme 3



unoptimised 58% yield. The stereochemistry shown in structure **20** for the synthetic protected macrolactin A followed from extensive analysis of its nmr spectroscopic data, and comparison and correlation with similar data recorded for the natural product. Unfortunately dearth of material did not permit us to fully study the deprotection of synthetic **20** to natural macrolactin A. Nevertheless, treatment of the macrocyclic MOM *bis*-methyl ether **20** with dimethylboron bromide (CH_2Cl_2, -78°C)[18] resulted in selective removal of the MOM group protection

producing **21a**, and further treatment of **21a** with the same reagent at -20°C led to a mixture of the isomeric mono-methyl ethers, **21b** and **21c**, of macrolactin A.[19] Thus, a novel strategy towards the triple 1,3-diene based macrolactin family of biologically important natural products, featuring sequential sp^2-sp^2 coupling (two inter- and one intra-molecular) reactions, has been realised, which should be applicable to a range of similar polyene macrolides.

ACKNOWLEDGMENTS

We thank Pfizer Central Research for financial support to purchase consumables for this project.

REFERENCES

1. Gustafson, K.; Roman, M; Fenical, W. *J. Am. Chem. Soc.*, **1989**, *111*, 7519; Rychnovsky, S.D.; Skalitzky, D.J.; Pathirana, C.; Jensen, P.R.; Fenical, W. *J. Am. Chem. Soc.*, **1992**, *114*, 671.
2. Benvegnu, T.; Schio, L.; Le Floc'h, Y.; Grée, R. *Synlett*, **1994**, 505; Donaldson, W.A.; Bell, P.T.; Wang, Z.; Bennett, D.W. *Tetrahedron Lett.*, **1994**, *35*, 5829; Tanimori, S.; Morita, Y.; Tsubota, M.; Nakayama, M. *Syn. Commun.*, **1996**, *26*, 559.
3. For reviews see: Stille, J.K *Angew Chem. Int. Engl.*, **1986**, *25*, 508; Mitchell, T.N. *Synthesis*, **1992**, 803; see also: Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.*, **1987**, *109*, 3785; Stille, J.K.; Su, H.; Hill, D.H.; Schneider, P.; Tanaka, M.; Morrison, D.L.; Hegedus, L.S. *Organometallics*, **1991**, *10*, 1993; Gyorkos, A.C.; Stille, J.K.; Hegedus, L.S. *J. Am. Chem. Soc.*, **1990**, *112*, 8465; Kalivretenos, A.; Stille, J.K.; Hegedus, L.S. *J. Org. Chem.*, **1992**, *56*, 2883.
4. Pattenden, G.; Thom, S.M. *Synlett*, **1993**, 215; see also Boden, C.; Pattenden, G. *Synlett*, **1994**, 181.
5. Some of the first examples of the intramolecular Stille reaction in synthesis were described by Piers *et al*, see: Piers, E.; Friesen, R.W.; Keay, B.A. *J. Chem. Soc., Chem. Commun.*, **1985**, 809; Piers, E.; Friesen, R.W. *J. Org. Chem.*, **1986**, *51*, 3405; Piers, E.; Lu, Y.-F. *J. Org. Chem.*, **1988**, *53*, 927.
6. See: Nicolaou, K.C.; Chakraborty, T.K.; Piscopio, A.D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.*, **1993**, *115*, 4419; Barrett, A.G.M.; Boys, M.L.; Boehm, T.L. *J. Org. Chem.*, **1996**, *61*, 685; McDermott, T.S.; Morlock, A.A.; Heathcock, C.H. *J. Org. Chem.*, **1966**, *61*, 700; Adlington, R.M.; Baldwin, J.E.; Gansäuer, A.; McCoull, W.; Russell, A.T. *J. Chem. Soc., Perkin Trans. 1.*, **1994**, 1697; Hodgson, D.M.; Boulton, L.T.; Naw, G.N. *Synlett*, **1995**, 267; Smith, A.B.; Condon, S.M.; McCaurley, J.A.; Leazer, J.L.; Leahy, J.W.; Maleczka, R.E. *J. Am. Chem. Soc.*, **1995**, *117*, 5407.
7. Millar, J.G.; Oehlschlager, A.C. *J. Org. Chem.*, **1984**, *49*, 2332.
8. All new compounds showed satisfactory spectroscopic data and mass spectrometric or microanalytical data.
9. Katsuki, T.; Lee, A.W.M.; Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Tuddenham, D.; Walker, F.J. *J. Org. Chem.*, **1982**, *47*, 1378.
10. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.*, **1986**, *108*, 7408.
11. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.*, **1991**, *113*, 9585.
12. Lane, C.F.; Myatt, H.L.; Daniels, J.; Hopps, H.B. *J. Org. Chem.*, **1974**, *39*, 3052.
13. Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc.*, **1987**, *109*, 813.
14. Miyuaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.*, **1979**, *20*, 3437; Miyuara, N.; Suiginome, H.; Suzuki, A. *Tetrahedron Lett.*, **1981**, *22*, 127; Miyuara, N.; Suiginome, H.; Yamada, Y.; Suzuki, A. *J. Am. Chem. Soc.*, **1985**, *107*, 972.
15. Uenishi, J.; Beau, J-M.; Armstrong, R.W.; Kishi, Y. *J. Am. Chem. Soc.*, **1987**, *109*, 4756.
16. Hodgson, D.M.; Boulton, L.T.; Maw, G.N. *Tetrahedron Lett.*, **1994**, *35*, 2231.
17. Alder, V-K.; Brochhagen, F.; Kaiser, C.; Roth, W. *Liebigs Ann. Chem.*, **1955**, *593*, 1.
18 Guindon, Y.; Morton, H.E.; Yoakim, C. *Tetrahedron Lett.*, **1983**, *24*, 3969.
19 These positional isomers were not fully separated and characterised.

(*Received in UK* 1 *March* 1996; *accepted* 22 *March* 1996)