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ENANTIOSPECIFIC AND DIASTEREOSELECTIVE SYNTHESIS OF C_{11}-C_{17} FRAGMENT OF TYLONOLIDE FROM "ASYMMETRIZED *TRIS* (HYDROXYMETHYL)METHANE"

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Summary : The fragment C_{11}-C_{17} of tylonolide **2** was straightforwardly and stereoselectively synthesized starting from monoacetate **5**, which is a synthetic equivalent of "asymmetrized *tris* (hydroxymethyl)methane" **3**.

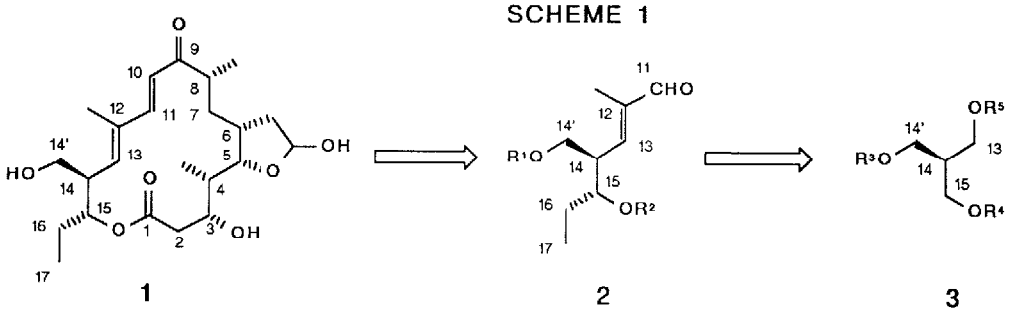
Tylonolide **1** is the aglicone of Tylosine, which is one of the most important macrolide antibiotics of the 16-membered-ring family and is extensively used today as a therapeutic agent. Its complex structure has been the object of several synthetic efforts by primary research groups.[1] In all the total syntheses reported to date, the chosen disconnections implied the involvement of C_{11}-C_{17} fragment **2** and its stereoselective preparation (Scheme 1).

We have recently reported that "asymmetrized *tris* (hydroxymethyl)methane" (THYM*) **3**, or its synthetic equivalents, successfully prepared by us through a chemoenzymatic strategy, represents a novel C-4 polyfunctionalised chiral building block that can be used for the synthesis of many natural products.[2] In this communication we describe the first practical exploitation of this new chiron as starting material in the straightforward synthesis of fragment **2** of tylonolide.

Monoacetate **5**, obtained in good yield and high e.e. from PPL catalysed hydrolysis of diacetate **4**,[2c] was converted, as previously described,[2b] into aldehyde **6** (Scheme 2).[3] The introduction of the second chiral centre present in **2** was then carried out through condensation with lithium diethylcuprate, which yielded the 2R,3R[4] compound **7a** in excellent yield and diastereoselectivity (see Table). This outcome is in agreement with the previously disclosed[2b] high asymmetric induction in Me_2CuLi addition to the same aldehyde. As a comparison, the Table shows also the results of condensation of **6** with other alkyl-metal compounds. Also for R= *n* Bu the best diastereomeric ratios were obtained using lithium dialkylcuprate in ether. A slight decrease of selectivity was observed on passing from methyl (95:5)[2b] to ethyl (93:7) to *n* butyl (87:13).

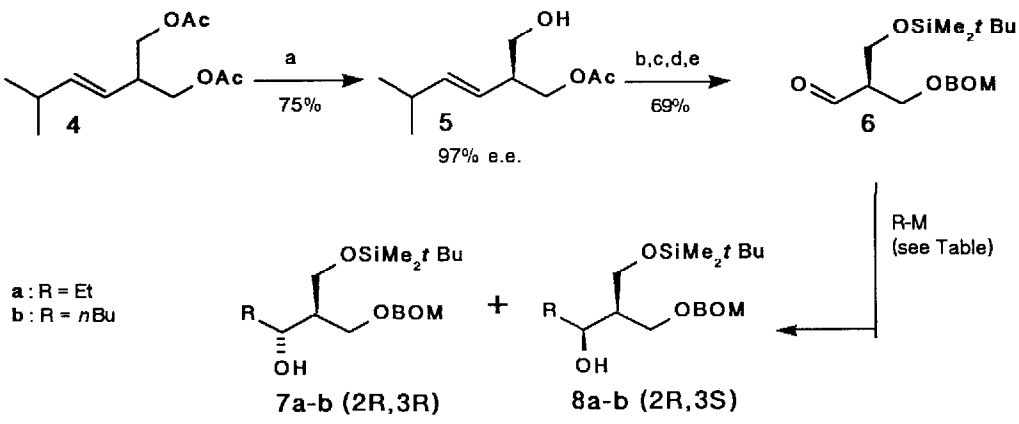
The major diastereoisomer **7a** was then converted into **13** and **19**, which are two differently

SCHEME 1



1 **2** **3**

SCHEME 2



a) PPL, H_2O//iPr_2O 85:15, pH 7 (see ref. 2c); b) tBuMe$_2$SiCl, DMF, imidazole, R.T.; c) 0.1 N KOH in MeOH, 87% (b+c); d) $PhCH_2OCH_2Cl$, $EtN(iPr)_2$, CH_2Cl_2, R.T., 86%; e) O_3, CH_2Cl_2, MeOH, -78°C; then Me_2S, R.T., 5h, > 92% (see note 3).

TABLE: Diastereoselection in alkyl-metal additions to aldehyde 6

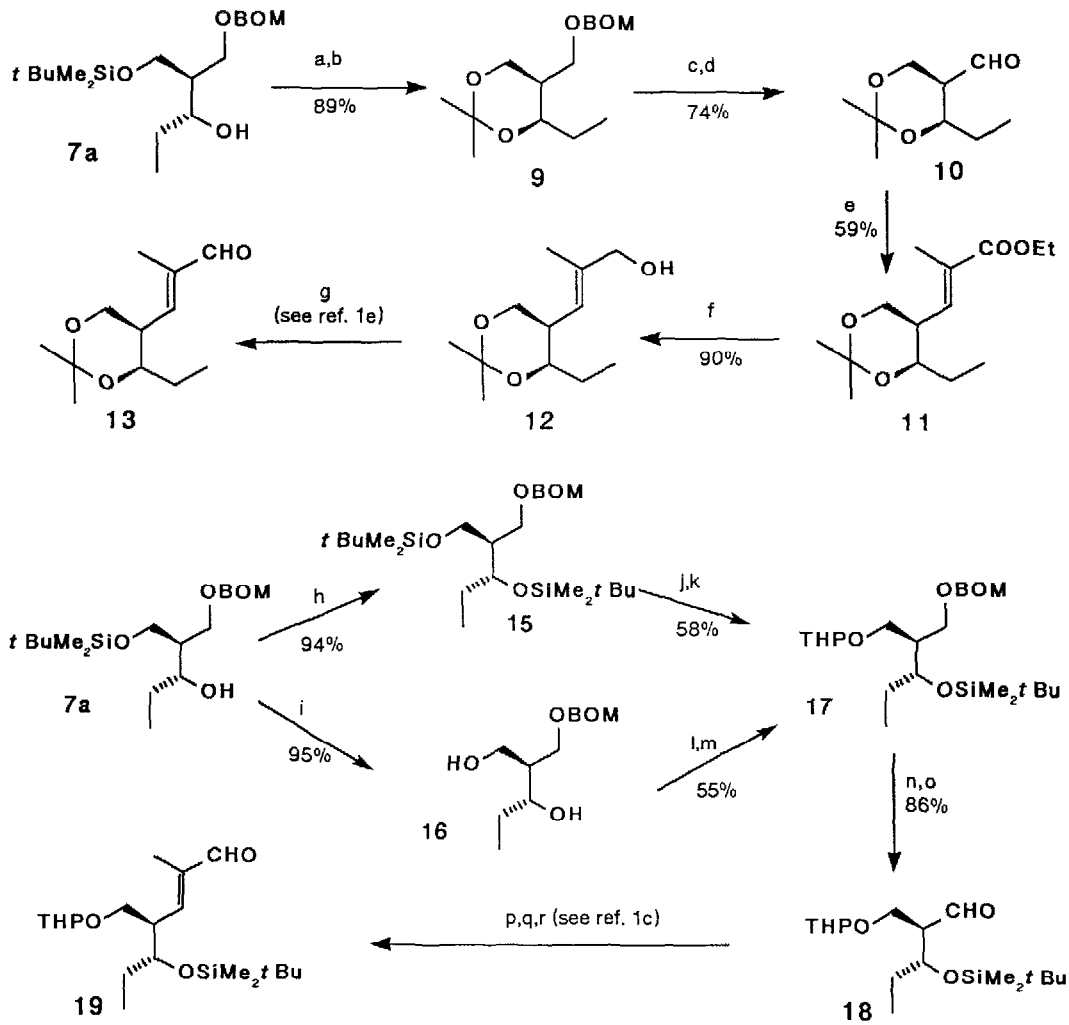
Entry	R-M	Solvent	Temperature	Yield	7 : 8 ratio[a]
1	Et-MgBr	Et_2O	-78°C	66%	74 : 26
2	EtCu•$MgBr_2$	Et_2O/Me_2S	-78°C	27% (54%)[b]	85 : 15
3	Et_2CuLi	Et_2O	-78°C→ -30°C	87%	93 : 7
4	nBuLi	Et_2O	-78°C	95%	59 : 41
5	nBu$_2$CuLi	Et_2O	-78°C→ -30°C	93%	87 : 13

a) determined by ^{1}H n.m.r. of crude products in the presence of Yb(FOD)$_3$; b) sluggish reaction: yield from non-recovered aldehyde is in brackets.

protected equivalents of our target **2** (Scheme 3); these two compounds have already been used as intermediates respectively by Grieco and Masamune in their total syntheses of **1**.[1e,1c] For the preparation of **13**, after uneventful transformation of **7a** into isopropylidene derivative **9**, the benzyloxymethyl group was removed through hydrogenolysis in buffered media. The presence of $CaCO_3$ was essential in order to avoid migration of the isopropylidene group. Oxidation of the resulting alcohol to the aldehyde **10** was efficiently carried out by the method recently developed by Ley and Griffith, which employs catalytic tetra-*n* -propylammonium perruthenate (TPAP) in conjunction with N-methylmorpholine N-oxide (NMO).[5] Finally Wittig condensation with the stabilized ylide (carbethoxyethylidene)triphenylphosphorane furnished in a complete stereoselective manner (no *Z* isomer detected) the enoate **11**, which was reduced to the alcohol **12** with DIBAH. Oxidation of **12** to the fragment **13** had already been described.[1e] It should be noted that, thanks to the interesting stereochemical properties of asymmetrized *tris* (hydroxymethyl)methane **3**, [2b] also **14**, which is the epimer of **12**, as well as their enantiomers can be prepared from **5** by the same number of steps (see note 6).

For the synthesis of **19** we had to solve a selectivity problem in the protective group interchange required for the conversion of **7a** into triprotected compound **17**. This transformation

SCHEME 3



a) *n*Bu_4NF•3 H_2O, THF, 95%; **b)** H_2C=C(Me)-OMe, *p*TSA, CH_2Cl_2, 0°C, 94%; **c)** H_2, Pd-C, $CaCO_3$, EtOH, 78%; **d)** (*n*$Pr)_4N^+$ RuO_4^-, N-methylmorpholine N-oxide, 4 Å molecular sieves, CH_2Cl_2, 95% (ref. 5); **e)** (carbethoxyethylidene)-triphenylphosphorane, toluene, reflux, 30h, 62%; **f)** DIBAH, CH_2Cl_2, -78°C, 90%; **g)** CrO_3•2 C_5H_5N, CH_2Cl_2, 0°C; **h)** *t*$BuMe_2$Si-OTf, 2,6-lutidine, CH_2Cl_2, 0°C, 94%; **i)** *n*Bu_4NF•3 H_2O, THF, 95%; **j)** pyridinium *p*-toluenesulfonate, EtOH, R.T., 3 days, 64%; **k)** dihydropyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, R.T., 7h, 91%; **l)** dihydropyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2, R.T., 7h, 60%; **m)** *t*$BuMe_2$Si-OTf, 2,6-lutidine, CH_2Cl_2, 0°C, 94%; **n)** H_2, Pd-C, $CaCO_3$, EtOH, 89%; **o)** (*n*-$Pr)_4N^+$ RuO_4^-, N-methylmorpholine N-oxide, CH_2Cl_2, 4 Å mol. sieves, 97% (ref. 5); **p)** Ph_3P=C(Me)-COOEt, toluene, 100°C, 12h; **q)** DIBAH, toluene, 0°C, 30 min.; **r)** CrO_3•2 C_5H_5N, CH_2Cl_2, R.T., 20 min.

was carried out in two ways, which proved to be equally efficient. The first method is based on the regioselective deblocking of primary silyl ether in **15**,[7] while in the second method the primary hydroxyl in diol **16** was selectively protected as tetrahydropyranyl ether. Triprotected derivative **17** was then smoothly hydrogenolized to give a primary alcohol which was in turn oxidized with TPAP and NMO[5] to aldehyde **18**. The transformation of this aldehyde into C_{11}-C_{17} fragment **19** through

Wittig condensation with Ph_3P=C(Me)COOEt followed by reduction and oxidation had already been described by Masamune.[1c]

It should be pointed out that the here described preparations of **13** (12 steps from monoacetate **5**) and **19** (13 steps from **5**) compare well with the previously reported ones (respectively 17 and 15 steps from the chosen starting chiral building blocks). Moreover most steps in our syntheses are simple and high yielding protective group interchanges.

In conclusion we have demonstrated that monoacetate **5**, which is a synthetic equivalent of "asymmetrized *tris* (hydroxymethyl)methane", is a perfectly suited chiral precursor for the C_{11}-C_{17} fragment of tylonolide, thanks to the diastereoselective addition of lithium diethylcuprate to aldehyde **6**. Other applications of **5** to the synthesis of biologically active substances are in progress in our laboratories.

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REFERENCES AND NOTES

1) Total syntheses: **a)** Tatsuta K., Amemiya Y., Kanemura Y., and Kinoshita M., *Tetrahedron Lett.*, **1981**, *22* , 3997; **b)** Nicolaou K.C., Pavia M.R., and Seitz S.P., *J.Am.Chem.Soc.*, **1982**, *104* , 2027; **c)** Masamune S., Kaiho T., and Garvey D.S., *J.Am.Chem.Soc.*, **1982**, *104* , 5521; **d)** Masamune S., Lu L.D.L., Jackson W.P., Kaiho T., and Toyoda T., *J.Am.Chem.Soc.*, **1982**, *104* , 5523; **e)** Grieco P.A., Inanaga J., Lin N.H., and Yanami T., *J.Am.Chem.Soc.*, **1982**, *104* , 5781; **f)** Tanaka T., Oikawa Y., Hamada T., and Yonemitsu O., *Tetrahedron Lett.*, **1986**, *27* , 3651; other approaches: Pearson A.J., Lai Y.S., Lu W., and Pinkerton A.A., *J.Org.Chem.*, **1989**, *54* , 3882; **h)** Y. Kitano, M. Kusakabe, Y. Kobayashi, and F. Sato, *Chem. Lett.* , **1986**, 523.

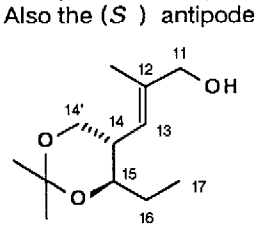
2) **a)** Guanti G., Banfi L., and Narisano E., *Tetrahedron Lett.* , **1989**, *30* , 2697; **b)** Guanti G., Banfi L., and Narisano E., *Tetrahedron Lett.* , **1990**, *31* , 6421; **c)** Guanti G., Banfi L., and Narisano E., *Tetrahedron: Asymmetry* , **1990**, *1* , 721.

3) Aldehyde **6** was not isolated, but used immediately for the next reaction; 92% was the estimated yield, based on the yield obtained after $NaBH_4$ reduction.

4) The enantiomeric purity of **7a** was checked through conversion into the two diastereo-meric Mosher's esters, by reaction with (R) or (S) methoxyphenyl(trifluoromethyl)acetyl chlorides (CH_2Cl_2, dimethylaminopyridine, R.T., 50-60% yield). These two diastereoisomers gave at ^1H n.m.r. distinct signals for the CH_3 protons of one of the two diastereotopic silicon bonded methyls. By integration we could measure an e.e. of 94%, indicating that negligible racemization had occurred.

5) Griffith W.P., Ley S.V., Whitcombe, and White A.D., *J. Chem. Soc., Chem. Commun.* , **1987**, 1625; Griffith W.P., and Ley S.V., *Aldrich. Acta* , **1990**, *23* , 13.

6) Also the (*S*) antipode of aldehyde **6** was easily obtained from **5** (see ref. 2b). **7a** was converted into **14** by the following sequence: **a)** H_2, Pd-C, $CaCO_3$,, EtOH; **b)** H_2C=C(Me)-OMe, *p* TSA, CH_2Cl_2, 0°C, 71% (2 steps); **c)** *n* $Bu_4NF \cdot 3\ H_2O$, THF, 89%; **d)** (*n* $Pr)_4N^+\ RuO_4^-$, N-methylmorpholine N-oxide, 4 Å mol. sieves, CH_2Cl_2, 95%; **e)** Ph_3P=C(Me)-COOEt, 4 Å mol. sieves, toluene, reflux, 3.5 h; **f)** DIBAH, toluene, -78°C, 62% (2 steps). The relative configuration of **12** and **14** was established by comparison of ^1H n.m.r. spectra: **12** had $J_{14\text{-}15}$ = 2.5 Hz. and $J_{14\text{-}14'}$ = 1.8 and 2.9 Hz., while **14** had $J_{14\text{-}15}$ = 8.9 Hz. and $J_{14\text{-}14'}$ = 7.4 and 9.7 Hz. These data clearly indicate a *cis* configuration for **12**.



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7) Cfr. C. Prakash, S. Saleh, and I.A. Blair, *Tetrahedron Lett.* , **1989**, *30* , 19; while the alternative mono-desilylation product of **15** was not detected in this solvolysis, moderate amounts of diol **16** were formed. Stopping the reaction at optimal reaction time we obtained 53% of desired product, 15% of **16**, and 17% of recovered **15** (64% is the yield from non-recovered starting material).

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