Pergamon

Tetrahedron Letters 39 (1998) 9513–9516

TETRAHEDRON LETTERS

Synthesis and Absolute Stereochemistry of Tanzawaic Acid (GS-1302)

Hirokazu Arimoto,* Kazuya Nishimura, Makoto Kuramoto,† and Daisuke Uemura††

Department of Chemistry, Faculty of Science, Shizuoka University, Ohya, Shizuoka 422, Japan
†*Advanced Instrumentation Center for Chemical Analysis, Ehime University, Bunkyou-chou 2-5, Matsuyama 790-77, Japan*
††*Department of Chemistry, Graduate school of Science, Nagoya University, Chikusa, Nagoya 464-01, Japan*

Received 19 August 1998; accepted 16 October 1998

Abstract:

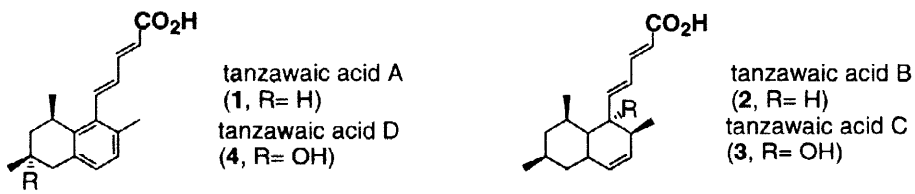
The first total synthesis of tanzawaic acid A(GS-1302-3) is described. The stereocontrolled synthetic route allowes the absolute stereochemistry to be determined. One key transformation in the sequence involves a Stille coupling with a highly hindered aryl triflate. Examples and results of several coupling reactions are also included.

keywords: Biologically active compounds; Stille coupling reactions; Stereochemistry; Carboxylic acids and derivatives

In our continuing search for biologically active substances from microorganisms, we reported tanzawaic acids (**1-4**), from *Penicillium citrium* SCRC-SA124.[1] The isolation of the tanzawaic acids was guided by an inhibition assay for superoxide anion production. This process is closely related to inflammation, cancer and aging.

Figure 1.

Structure of Tanzawaic acids



Among these compounds, **1** and **2** had been patented as antimicrobial agents(GS1302-3 and -1 respectively) by Kyowa Hakko Kogyo.[2] Tanzawaic acids, GS-1302s, and anticoccidal hynapens,[3] which were all isolated from *Penicillium sp.*, share a novel polyketide-type skeleton. The absolute stereochemistry of these compounds have remained elusive until now. Wide and intriguing biological activities prompted us to examine the stereochemistry by a total synthesis.

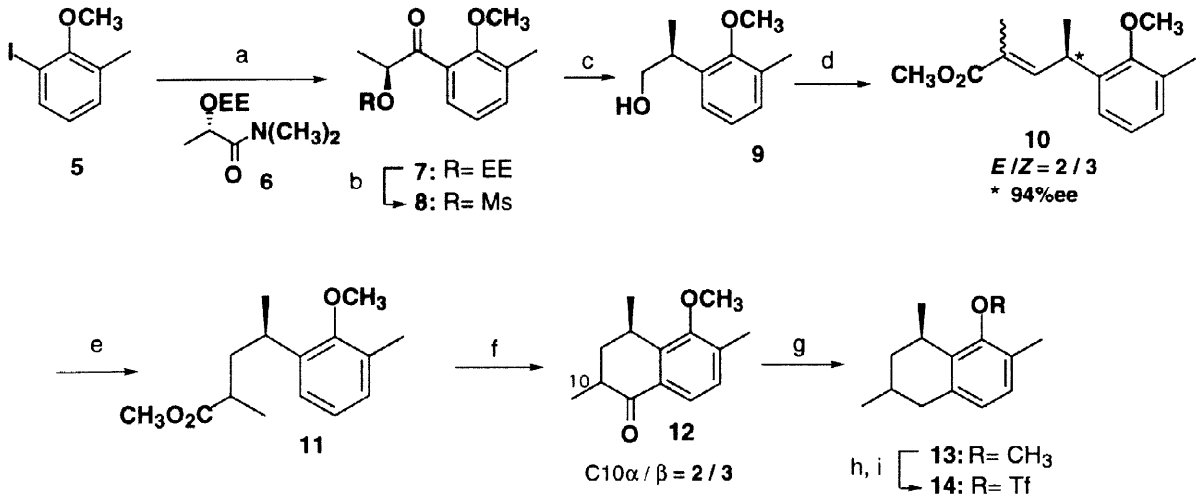
Our synthesis began with a protected iodocresol **5**(Scheme 1). The aryl iodide was condensed with lactamide **6** via halogen-lithium exchange. Acidic hydrolysis and mesylation afforded an α-mesyloxy ketone **8**,

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02226-6

which was subjected to Suzuki-Tsuchihashi's reductive pinacol rearrangement[5] to give desired alcohol **9**($[\alpha]_D^{28}$ -9.1°, *c* 1.0 in $CHCl_3$).[6] Lewis acid additives employed in the original procedure, such as Et_3Al or Et_2AlCl, were not necessary for smooth conversion, and optimal yields. This phenomenon may be due to the ortho-methoxy substitution effect, which was not investigated in the original works.

Swern oxidation of **9** provided the aldehyde which was immediately converted to a geometrical mixture of α,β-unsaturated ester (*E*:*Z*, 2:3) by a Horner-Emmons reaction.[7] At this stage, diastereoselective reduction of the carbon-carbon double bond for both the (*E*) and (*Z*)- isomers were investigated, unfortunately without success. The mixture of the unsaturated esters **10** were therefore hydrogenated to **11**. The esters was transformed to the corresponding acid chloride and subjected to Friedel-Crafts cyclization conditions to form **12**. Deoxygenation of ketone **12** was achieved by catalytic hydrogenation without difficulty. Cleavage of the methyl ether with BBr_3 followed by sulfonylation gave the key intermediate aryl triflate **14** (α:β, 2:3).

Scheme 1.
Synthesis of aryl triflate 14.



Reagents and conditions: (a) *n*-BuLi, -78°C then **6** / THF, -78°C to room temp. (89%); (b) i) 1M HClaq. ii) MsCl, Pyr., -55°C, CH_2Cl_2 (85% in 2 steps); (c) DIBAL-H(2.5eq.), CH_2Cl_2, -78°C to 0°C (63%); (d) i) Swern oxidation, -78°C, ii) $(MeO)_2P(O)CH(CH_3)CO_2Et$, KHMDS, 18-crown-6 / THF (84%); (e) H_2, Pd-C / MeOH (quant.); (f) i) LiOH / THF- CH_3OH -H_2O(2:1:1), ii) $(COCl)_2$, cat. DMF, CH_2Cl_2, iii) $AlCl_3$ / CH_2Cl_2, 0°C to room temp. (91%); (g) H_2, Pd-C / CH_3OH (quant.); (h) BBr_3 / CH_2Cl_2, -78°C to room temp.(99%); (i) Tf_2O, (*i*-Pr)$_2$NEt / CH_2Cl_2, -78°C to room temp.(quant.).

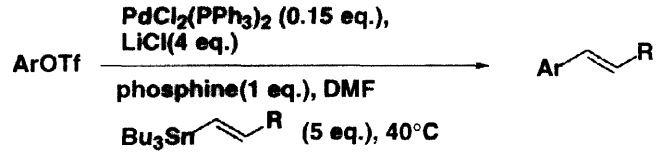
The Stille coupling was then investigated. An online reaction search using Beilstein database indicated *no example of a Stille coupling with sterically demanding o, o'-dialkyl substituted aryl triflate*, when at least one of the substituents is secondary. In fact, reactivity of model triflates(**18**, **19**, **14**) with dienostannane **21** decreased rapidly as the number of the substitutions around reaction center increased under the standard Stille conditions (Table 1, entry 1-3).

At this stage, we decided to use vinyl stananne **22**, due to the instability of dienostanane **21** under reaction conditions. After months of the extensive investigations,[8] we were encouraged to find that trace amounts of coupling product **15** were formed(entry 6) by preheating $PdCl_2(PPh_3)_2$ with both $(o\text{-tol})_3P$ and the triflates *before* the addition of vinyl stannanes. Warming the entire mixture caused rapid decomposition of the vinyl stannane and no coupling product was obtained. In contrast to the general mechanistic scheme,[9] where a transmetalation of a stannane is the rate limiting step, we assumed that the oxidative addition of the triflate to palladium(0) species was so slow due to steric hindrance. The undesired side reaction of palladium(II) catalyst

with stananes would lead to the formation of the stanyl salt which is known to deter the reaction. Actually, upon the addition of a tin scavenger, $Ph_2P(O)ONBu_4$, developed by Liebeskind,[10] the yield was drastically improved up to 17%(entry 8). Interestingly, the reaction was stereoselective, and the coupled product was predominantly the β-isomer at C10(α: β, 1: >9).[11] The triflate starting material was a 2:3 (α: β) mixture, therefore the yield based on only the β-triflate, was about 25%. No other products derived from the α or β-triflate were found in the reaction.

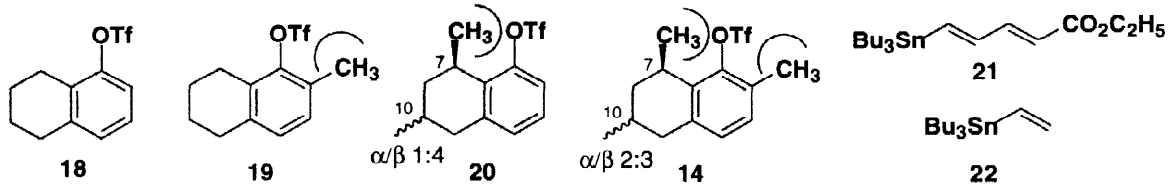
Table 1.

Stille coupling of Aryl triflates with Vinyl stannanes.



entry	stannane	aryl triflate	tin scavenger[d]	time(hr)	product (yields, %)
1[a]	21	18	—	16	61
2[a]	21	19	—	20	12
3[a]	21	14	—	75	-
4[b]	22	18	—	20	51
5[b]	22	20	—	2	42[e]
6[b]	22	14	—	19	trace
7[b]	22	14	$Ph_2P(O)ONBu_4$	32	10[f]
8[b,c]	22	14	$Ph_2P(O)ONBu_4$	40	17[f]

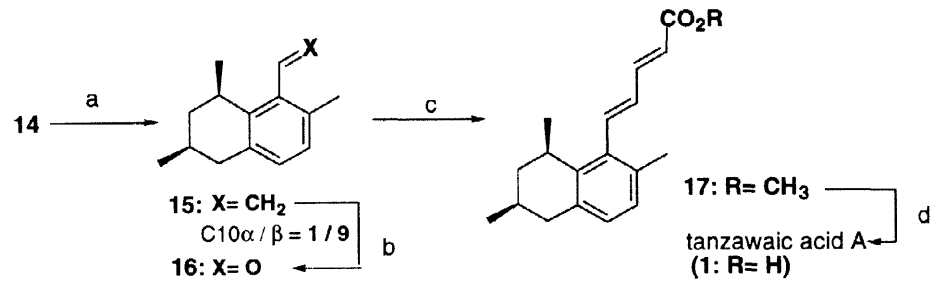
a) Triphenylphosphine was used.
b) *o*-Tolylphosphine was used.
c) NMP was used as a solvent.
d) 0.12 eq.
e) A diastereomeric ratio(α/β) of the coupling products at C10 was 1:8.
f) A diastereomeric ratio(α/β) of the coupling products at C10 was 1:9.



Although the yield remains to be improved, the above findings allowed us to conduct following transformations to **1** (Scheme 2).

Scheme 2.

Synthesis of Tanzawaic Acid A.



Reagents and conditions: (a) see table 1; (b) OsO_4, $NaIO_4$, THF-H_2O(1:2), (31%); (c) $(MeO)_2P(O)CH_2CHCHCO_2CH_3$, NaH, DME (60%); (d) LiOH / THF-CH_3OH-H_2O (quant.).

First, the oxidative cleavage of an olefin with OsO_4-$NaIO_4$ conditions afforded **16**. This aldehyde was treated with Horner-Emmons reagent followed by basic hydrolysis gave **1**, tanzawaic acid A(GS-1302-3), which could be separated from its C10 epimer via HPLC (ODS; MeOH:H_2O:TFA, 90:10:0.1). The proton NMR and specific rotation were in good agreement with those of the authentic sample.[12] This evidence supports the absolute stereochemical assignment of tanzawaic acids and GS-1302s depicted in figure 1.

In conclusion, we accomplished the first total synthesis of tanzawaic acid A(GS-1302-3). The stereocontrolled route allows the absolute stereochemistry to be determined. A key step involved the use of Liebeskind's tin scavenger in a Stille coupling with a highly hindered aryl triflate. These new conditions may have general synthetic utility.

Acknowledgments

The authors thank Dr. G. Ott and Dr. M. Pedersen-Morris for helpful discussions and for critiquing the manuscript. This research was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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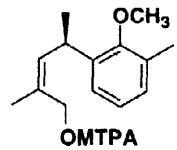
[6] The alcohol **9** was proved to be optically pure as evidenced by ^1H NMR study of the corresponding (*R*) and (*S*)-MTPA esters.

[7] The geometrical mixture of α,β-unsaturated esters could be separated via repetitious column chromatography. The (*Z*)-isomer was reduced with DIBAL-H to an allyllic alcohol, which was converted to its MTPA ester **22**. The enantiomeric excess of **10** was 94% e.e. as determined by ^1H NMR of **22**.

(*Z*)- **10** → 1) DIBAL-H, 2) (*S*)-MTPACl → 

22

[8] Conditions using $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ as a catalyst, failed, even in the presence of a tin scavenger (*vide infra.*).

[9] Farina V, Krishnamurthy V, Scott WJ, Org. React 1997; 50;1-652.

[10] Srogl J, Allred GD, Liebeskind LS. J. Am. Chem. Soc. 1997;119:12376-12377.

[11] It is unclear at this point why we see the formation of predominantly the β-isomer for entries 5, 7 and 8. The stereochemistry at C10 should control the orientation of C7 methyl group. This may influence the ease of approach of the palladium catalyst.
The effects of the Liebeskind's tin scavenger on highly hindered aryl triflates is under investigation in this laboratory, results will be reported in due course. However, no coupling product from o, o'-di-*sec*-alkyl substituted triflate has yet been observed.

[12] ^1H NMR of synthetic **1**(400MHz, $CDCl_3$), δ 1.06(3H, d, *J*= 6.6 Hz), 1.06(1H, m), 1.14(3H, d, *J*= 6.9 Hz), 1.65(1H, m), 2.14(1H, m), 2.28(3H, s), 2.34(1H, m), 2.62(1H, ddd, *J*= 3.4, 3.4, 14.7 Hz), 3.21(1H, m), 5.96 (1H, d, *J*= 15.4 Hz), 6.42 (1H, dd, *J*= 11.0, 15.8 Hz), 6.93(1H, d, *J*= 7.7 Hz), 6.97(1H, d, *J*= 7.7 Hz), 7.09 (1H, d, *J*= 15.8 Hz), 7.55 (1H, dd, *J*= 11.0, 15.4 Hz);
In our preliminary report on the isolation of tanzawaic acids,[1] we actually reported the specific rotation of the sodium salt of tanzawaic acid A($[\alpha]_D$ +53° in CH_3OH), instead of natural tanzawaic acid A as noted. The correct value for natural tanzawaic acid A {$[\alpha]_D^{28}$ +147° (*c* 0.04 in $CHCl_3$)} is in good agreement with both GS-1302-3 {$[\alpha]_D$ +145° (*c* 0.101 in $CHCl_3$)}[2], and the synthetic sample {$[\alpha]_D^{28}$ +140° (*c* 0.15 in $CHCl_3$); 94% e.e.(see footnote 6)}.