Tetrahedron 71 (2015) 7204–7208

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Geometry-selective synthesis of the unsaturated side chains of the isodomoic acids

Nadia Fleary-Roberts, Gilles Lemière, Jonathan Clayden *

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

ARTICLE INFO

Article history:
Received 30 October 2014
Received in revised form 5 February 2015
Accepted 16 February 2015
Available online 20 February 2015

Keywords:
Alkene
Coupling
Metalcatalysed
Natural product synthesis

ABSTRACT

Three unsaturated vinylic or allylic halides were made in enantiomerically pure form, ready for coupling with a vinyl metal as part of a divergent strategy for the synthesis of members of the domoic/isodomoic acid family and their analogues. The trisubstituted alkene **3** was made by an *E*-selective Wittig reaction, while **4** and **5** were made by stereoselective hydrometallation or hydroboration of an alkyne.

1. Introduction

Domoic acid and the isodomoic acids (Scheme 1) are a series of metabolites produced by marine algae *Chondria armata* and *Pseudonitzschia* spp.[1] They have neurological activity as glutamate analogues, and domoic acid has been implicated as the causative agent of amnesic shellfish poisoning.[2] As a result, its toxicology has been widely studied in humans and marine animals. More detailed binding studies have revealed differences between the binding affinity of some of the isodomoic acids for their targets, the kainate subfamily of ionotropic glutamate receptors. However, the limited supply of the natural products has hampered detailed exploration in this area.

An alternative source of domoic acid and the isodomoic acids is provided by total synthesis. (−)-Domoic acid was synthesised in 1982 by Ohfune;[3] our group has reported syntheses of (−)-isodomoic acids B,[4] C,[5] E,[4] and F;[4] the groups of Mongomery[6] and Denmark[7] have reported synthesis of (−)-isodomoic acids G and H.

The isodomoic acids are all double bond regio- and stereoisomers with the same constitutional formula, and five of them, along with domoic acid, share the same three unsaturated side chains, as shown in Scheme 1. Our strategy for the synthesis of isodomoic acids B, E and F, which could in principle be extended to isodomoic acids A and D and domoic acid itself, was to synthesise a core alkyne **1** and to functionalise this to give either *Z*- or *E*-**2** by stereoselective carbometallation (*Z* selective for isodomoic acids A, D and domoic acid; *E* selective for isodomoic acids B, E and F). We have realised this aim in palladium-catalysed couplings of the *E*-stannane *E*-**2** (Met=$SnBu_3$) resulting from *cis*-stannylcupration and methylation of **1**, which allowed the synthesis of (−)-isodomoic acids B, E and F.[4] Similar routes isodomoic acids A, D and domoic acid are awaiting the development of a suitable method for trans-carbometallation of **1** to give *Z*-**2**. This divergent strategy could also provide, in a simple manner, analogues of the domoic acid family for further biological evaluation.

Central to the effectiveness of the strategy are practical routes to the coupling partners **3**, **4** and **5** in geometrically and (for **4** and **5**) enantiomerically pure form. Brief details of our syntheses of these compounds were provided previously,[4] but in this paper we describe the optimisation of routes to these side chains, and their syntheses in quantities sufficient for ligation to a vinylmetal coupling partner. For reasons of practicality in the final deprotection step, *tert*-butyl ester protecting groups were used for all the carboxylic acid functions, since the route to the alkyne **1**[4] necessitates the use of *tert*-butyl ester protection.

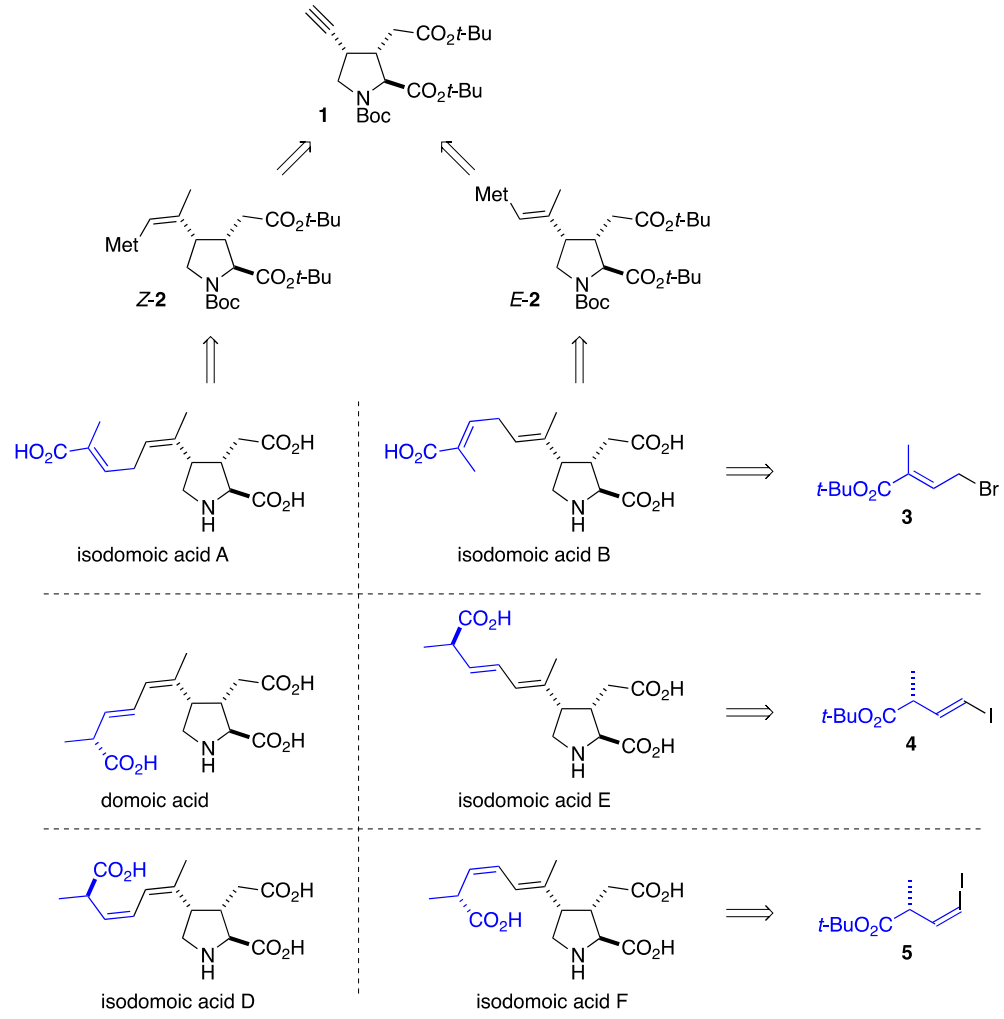
2. Results and discussion

2.1. Synthesis of 3

A synthesis of the methyl ester analogous to **3** has been reported, and **3** was conveniently made by a modification of this route.[8a] *tert*-Butyl 2-bromoproprionate **6** was converted to a phosphonium salt and treated with glyoxylic acid under basic conditions to provide the half-ester **7** as its *E* isomer with complete

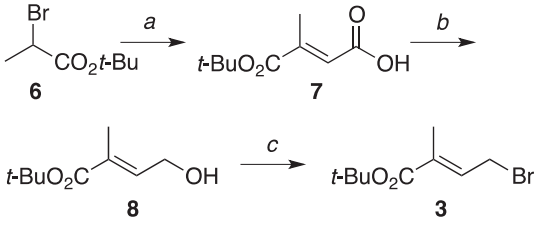
* Corresponding author. E-mail address: clayden@man.ac.uk (J. Clayden).

http://dx.doi.org/10.1016/j.tet.2015.02.055
0040-4020/



Scheme 1. Divergent strategy for the synthesis of the domoic/isodomoic acid family.

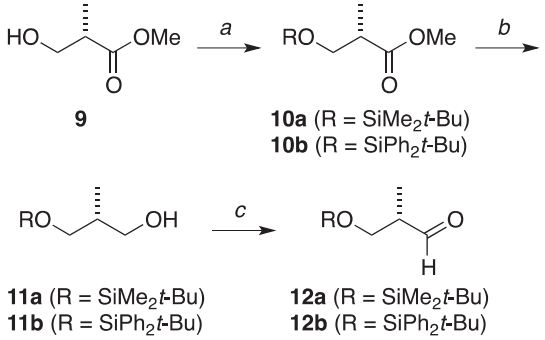
geometrical selectivity, though in lower yield and more slowly than the corresponding methyl ester (Scheme 2). Reduction with borane dimethyl sulfide complex gave alcohol **8**, which was brominated with phosphorus tribromide to afford protected side chain **3**.



Scheme 2. Synthesis of **3** by *E*-selective Wittig reaction. Reagents and conditions: *a* (i) PPh_3, MeCN, 65 °C, 24 h; (ii) glyoxylic acid monohydrate, EtN^iPr_2, MeCN, 0 °C to rt, 72 h (33%); *b* $Me_2S{\cdot}BH_3$, THF, rt, 16 h (68%); *c* PBr_3, CCl_4, 0 °C, 2 h, (21%).

2.2. Synthesis of 4 and 5

The geometrical isomers of the enantiomerically pure vinyl iodides **4** and **5** were envisaged as divergent derivatives of a single common starting material, the aldehyde **12**, which would be olefinated with either *E* or *Z* selectivity. The aldehyde **12** was itself made from (*S*)-Roche ester **9** as shown in Scheme 3.[8b] Protection of the hydroxyl group as either its TBDMS or TBDPS ether gave the esters **10a** and **10b**. Attempts to effect a reported partial reduction



Scheme 3. Synthesis of the aldehydes **12a** and **12b**. Reagents and conditions: For **10a** *a* ^{t}BuMe$_2$SiCl, DMAP, Et_3N, CH_2Cl_2, 12 h, rt, 94%; for **10b** *a* ^{t}BuPh$_2$SiCl, imid., DMF, 0 °C, 2 h, 98%; *b* **11a** DIBAL (2 equiv), tol, −40 °C, 3 h, 82%; **11b**: DIBAL (2.5 equiv), CH_2Cl_2, −40 °C, 2 h, 98%); *c* $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 °C, 1 h 30 min (**12a**: 61%; **12b**: 88%).

of esters **10** directly to the aldehydes[8c] **12** with DIBAL were unsuccessful, so instead a two-step procedure was used: the reaction of 2.5 equiv of DIBAL gave the alcohols **11a** and **11b**, and Swern oxidation returned the aldehydes **12a** and **12b**. We found that the TBDPS protecting group gave much better yields than the TBDMS group, possibly because of the volatility of the TBDMS-protected compounds.