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Synthesis of (−)-Amphidinolide K Fragment C9−C22

Thanos Andreou, Anna M. Costa, Laia Esteban, Lluïsa Gonzàlez, Gemma Mas, and Jaume Vilarrasa*

Departament de Química Orgànica, Facultat de Química, Av. Diagonal 647, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain

jvilarrasa@ub.edu

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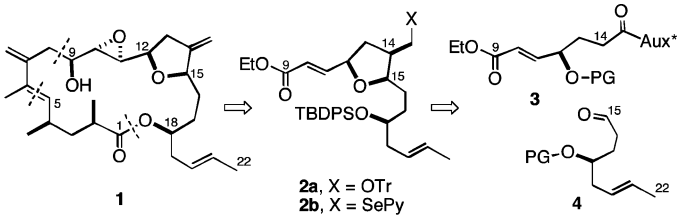
ABSTRACT

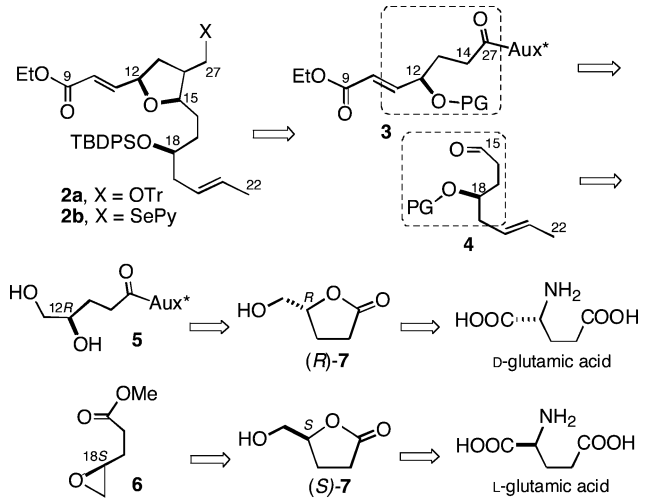


The key fragment (2a or 2b) in a total synthesis of the cytotoxic macrolide (−)-amphidinolide K (1) has been achieved from synthons C9−C14 (3) and C15−C22 (4), which have both been prepared from glutamic acid in good overall yields.

Amphidinolide K is a macrolide isolated by Kobayashi et al. from a laboratory-cultured dinoflagellate *Amphidinium* sp.; it shows strong cytotoxic activity against murine lymphoma L1210 and epidermoic carcinoma KB cells[1] and as such is of interest to those involved in anticancer drug design. The structure of amphidinolide K (established from 0.3 mg of sample!) was originally reported with some uncertainties regarding the relative stereochemistry at C2, C4, and C18. Several years ago, we embarked on the syntheses of different stereoisomeric fragments of this gross structure, with the aim of finding analogues (or libraries of analogues) of similar or higher cytotoxicity. During this period, Williams and Meyer reported on a synthesis of the C7−C22 segment[2a] and later accomplished a synthesis of (+)-amphidinolide K and several stereoisomers,[2b] which allowed the absolute configuration of the natural product to be deduced. (−)-Amphidinolide K has the structure **1**.

In previous work, we developed a route to a potentially useful C1−C5 building block.[3] We report here on our approach to synthons **2a** and **2b** (*cis*-2,5-disubstituted) from two key fragments: the C9−C14 + C27 segment (hence-forward C9−C14, or **3**) and the C15−C22 intermediate **4**. The synthesis was designed with the underlying ideas of versatility and simplicity. As shown in Scheme 1, it is based on a stereocontrolled aldol-like reaction between **3** and aldehyde **4**, as well as on a simple S_N2-like cyclization

Scheme 1



(1) Ishibashi, M.; Sato, M.; Kobayashi, J. *J. Org. Chem.* **1993**, *58*, 6928.
(2) (a) Williams, D. R.; Meyer, K. G. *Org. Lett.* **1999**, *1*, 1303. (b) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765.
(3) Mas, G.; Gonzàlez, L.; Vilarrasa, J. *Tetrahedron Lett.* **2003**, *44*, 8805.

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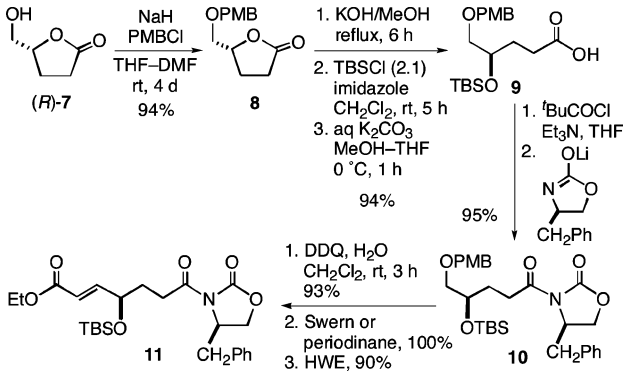
reaction (hydroxyl at C12, leaving group at C15) to create the five-membered ring. The five carbon atoms highlighted in **3** and **4** may arise from **5** and **6**, respectively, which in turn may come from the corresponding enantiomers of glutamic acid or their synthetically equivalent 5-hydroxymethyltetrahydrofuran-2-ones (**7**). Both enantiomers of **7** are commercially available, at the same price.

Thus, stereoisomers of **2a** or **2b** would be synthesized using the same protocols. Employing either butyrolactone as a starting material, varying the chiral auxiliary used in the aldol reaction, and carrying out the cyclic ether formation either way (leaving group at C12 and hydroxyl at C15 or vice versa) would allow one to achieve alternate configurations at C12, C15, and/or C18. In other words, the outlined strategy is in principle really versatile.

Conversion of (*R*)-**7** into an appropriate derivative of **5** was first investigated (Scheme 2). Protection of the hydroxy

Scheme 2

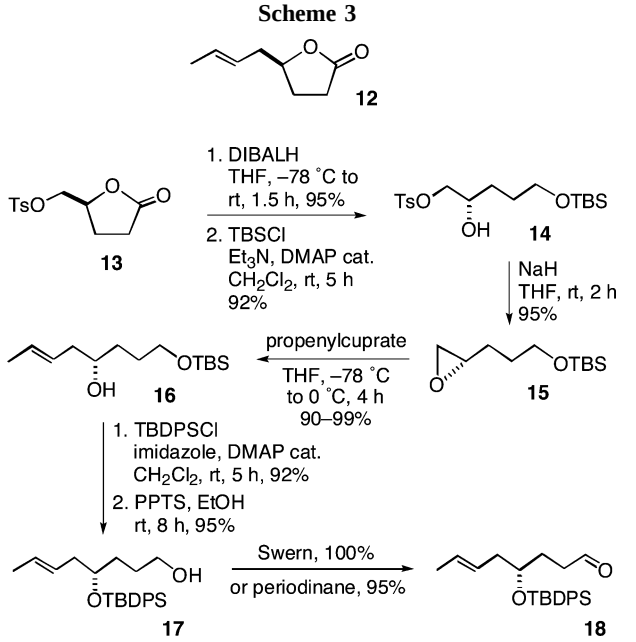


group of (*R*)-**7** as a *p*-methoxybenzyl ether (**8**),[4] opening of the lactone with base, and silylation of the alcohol with *tert*-butyldimethylsilyl chloride in two steps gave **9**. Activation of the carboxyl group in **9** in the usual way and reaction with the lithium salt of (*R*)-4-benzyl-1,3-oxazolidin-2-one[5] at −78 °C for 2 h in THF and 0 °C for 10 h gave the C11−C14 fragment **10** in 95% yield, ready to be subjected to the desired aldol reactions.[6] After removal of the PMB group from **10** with DDQ (H_2O, CH_2Cl_2, rt, 3 h),[4] oxidation of the alcohol under Swern conditions (Me_2SO/ClCOCOCl, CH_2Cl_2, −78 °C, then Et_3N)[7a] or using the Dess−Martin periodinane (1.5 equiv, CH_2Cl_2)[7b] gave the aldehyde with excellent results. However, the Swern reaction turned out to be more practical on a larger scale (lower price of the reagents, shorter reaction times, purification by chromatography unnecessary). A Horner−Wadsworth−Emmons reaction ($EtOCOCH_2PO(OEt)_2$, BuLi, DME, rt, 6 h)[8] thereafter gave the C9−C14 fragment **11** (cf. **3**). The overall yield from **7** to **11** was 70%.

The synthesis of the C15−C22 fragment was first attempted according to the strategy shown in Scheme 1. Methyl (*S*)-4,5-epoxypentanoate (**6**) was prepared from (*S*)-**7**[9] by tosylation and ring opening with sodium methoxide. The organocuprate prepared from (*E*)-1-bromopropene, Li,[10] and CuCN was active on an epoxide model but gave a complex mixture of products when reacted with **6** and starting material was also recovered. The desired product (isolated as its lactone **12**) was obtained in poor yields (ca. 30%). Coupling of the organocuprate prepared from (*E*)-1-propenyl-1-lithium and typically CuI or CuCN with the *O*-tosyl derivative **13** (commercially available), to reach **12** in an alternative way, was also unsuccessful. Thus, we decided to replace epoxyester **6** with the corresponding epoxyalcohol,[11] protected as a silyl ether.

Reaction of **13** with an excess of DIBALH, protection of the primary alcohol as its TBS ether (**14**), and treatment with NaH in THF afforded **15** as shown in Scheme 3.[12] Addition

Scheme 3



of the organocuprate of (*E*)-1-propenyl-1-lithium (2 mol per mol of CuCN) gave the desired product, **16**, in 99% isolated

(4) Cf. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999, and references therein.

(5) (a) Cage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77. (b) Evans, D. A.; Urpí, F.; Sommers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

(6) On the other hand, opening of the lactone ring of **7** with (*R,R*)-pseudoephedrine and protection/activation of the vicinal diol as a sulfite ester, followed by reaction with 3-methylbutanal (as a model) and tetrahydrofuran ring formation with NaH posed diverse problems, such as a moderate yield of the aldol reaction and no cyclization in the last step. Use of a stronger EWG−sulfate instead of sulfite−posed problems also, i.e., poor yields of the sulfate preparation and a premature elimination reaction.

(7) (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(8) Review: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

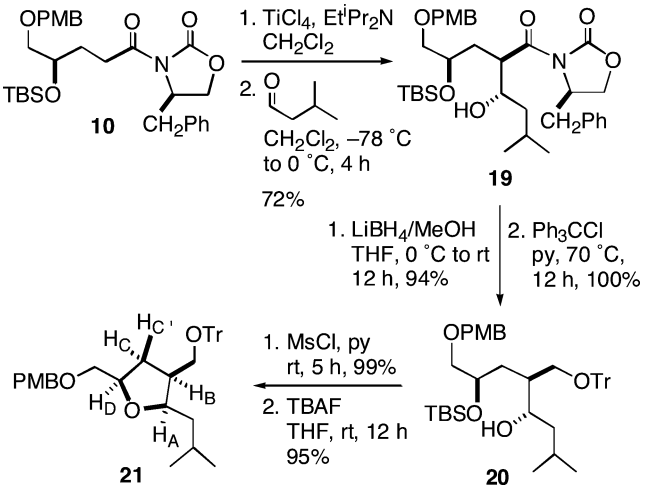
(9) Compound (*S*)-**7** is usually obtained through diazotization of L-glutamic acid, lactonization, and reduction of the carboxyl group with borane (or related procedures). See: (a) Lehmann, J.; Pieper, B. *Tetrahedron: Asymmetry* **1992**, *3*, 1537. (b) Figadère, B.; Harmange, J.-C.; Laurens, A.; Cavé, A. *Tetrahedron Lett.* **1991**, *32*, 7539 and references therein. For an alternative synthesis of **6** from D-mannitol, see: (c) Chattopadhyay, S.; Mamdapur, V. R.; Chadha, M. S. *Tetrahedron* **1990**, *46*, 3667.

yield. Use of lithium [cyano(*E*-1-propen-1-yl)(2-thienyl)-cuprate][13] afforded **16** in 90% yield but now expended only 1 mol of (*E*)-1-bromopropene per mol of the commercially available Li[Cu(CN)(2-thienyl)].

Protection of the hydroxy group in **16** as its *tert*-butyldiphenylsilyl ether and selective removal of the TBS group with pyridinium tosylate (PPTS) gave **17**. Oxidation to **18** was carried out by standard procedures. The overall yield of **18** (cf. **4**, PG = TBDPS) from **7** was 68%.

The intended aldol reaction between **18** and **10** was first probed on a model setting using substrate **10** and 3-methylbutanal (Scheme 4). Via the chlorotitanium enolate derived

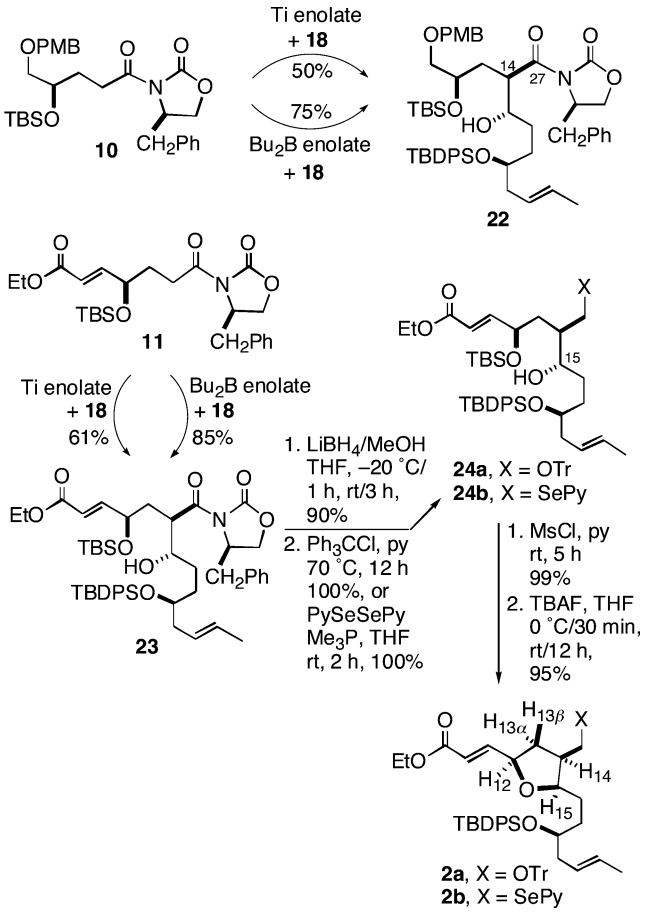
Scheme 4



from **10** (with $TiCl_4$),[6b] only one aldol diastereomer (**19**) was obtained in 72% yield.[14] The configuration of the carbon atom α to the COAux* (C14) was not important, as a double bond would later be installed between C14 and C27. Nevertheless, only the expected *syn* adduct was detected. Reduction of **19** with $LiBH_4$/MeOH in THF, to give the diol, protection of the primary alcohol as its trityl ether **20**, and activation of the secondary alcohol in **20** as a methanesulfonyl derivative (MsO group) took place smoothly. Treatment of this mesylate with $Bu_4N^+F^-\cdot 3H_2O$ (TBAF) thereafter induced tetrahydrofuran ring formation in excellent yield, leading to model compound **21**; its relative stereochemistry was established by a NOESY experiment.

The reactivity of various enolates derived from **10** and the more advanced intermediate **11** were then compared (Scheme 5). Using the titanium enolate of **10** ($TiCl_4$, Et^iPr_2N, CH_2Cl_2)[14a] and aldehyde **18** (addition at −78 °C, then 5 h at room temperature), 50% of stereopure **22** was isolated, whereas with the dibutylboron enolate of **10** (Bu_2BOTf, Et_3N, CH_2Cl_2) and aldehyde **18** (addition at −78 °C, then 5 h at 0 °C) an improved product yield of 75% (with recovery of 15% and 20% of **10**, respectively) was observed.[15]

Scheme 5



Application of the two enolization protocols to **11** and **18** (Scheme 5) provided **23** as a single diastereomer, in 61%

(10) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.

(11) Conversion of **6** to the corresponding epoxyalcohol with titanium tetraisopropoxide and polymethylhydrosiloxane (Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1995**, *60*, 7884) was not useful as the 4,5-epoxy-1-pentanol isomerized to 5-hydroxymethyloxolane (THF derivative) under the reaction conditions, as might be expected.

(12) For related procedures, see: (a) Nagumo, S.; Furukawa, T.; Ono, M.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 2849. (b) Harrowven, D. C.; Dennison, S. T.; Hayward, J. S. *Tetrahedron Lett.* **1994**, *35*, 7467.

(13) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(14) (a) To avoid a partial cleavage of the acid-sensitive groups, the reagents were added to **10** as follows: 0.1 equiv of Et^iPr_2N (DIPEA), then 1.2 equiv of $TiCl_4$, and finally 1.1 equiv of DIPEA. (b) Enolization with $TiCl_3(O^iPr)$ afforded a mixture of two aldols: Mas, G. PhD Thesis, Universitat de Barcelona, 2000. (c) When parallel aldol-like reactions were carried out in our lab with thiazolidine-2-thione chiral auxiliaries (instead of the oxazolidin-2-one derivatives shown in Schemes 2 and 4), the results were disappointing: Batlle, M. Master's Thesis, Universitat de Barcelona, 2003. For leading references on thiazolidine-2-thione auxiliaries, see: (d) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun*. **1985**, 1418. (e) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391 [acetate aldol reactions of Sn(II) enolates]. (f) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604 and references therein (preparation). (g) González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949 (acetate aldol reactions of Ti enolates). Also see: (h) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883 (Ti enolates of oxazolidine-2-thione derivatives). (i) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894 and references therein. For a review, see: (j) Evans, D. A.; Shaw, J. T. *Actualité Chim.* **2003**, 35.

(15) For the cleavage of the final boron complexes, in all cases the reaction mixtures were quenched at low temperature with MeOH and buffered water (pH 7). The resulting solutions or suspensions were stirred for ca. 12 h (no hydrogen peroxide or bases were added).

yield for $TiCl_4/Et^iPr_2N$ conditions, and 85% yield for Bu_2BOTf/Et_3N conditions (15% of **11** was recovered in both cases, so that the conversion was ca. 75% and ca. 100%, respectively).[14a,15] After several trials, reduction of the complex multifunctionnal substrate **23** to its diol could be accomplished with $LiBH_4$ (220 mol %) in the presence of MeOH (250 mol %),[16] in such a way that only 5−7% reduction of the conjugate double bond took place, while the C20−C21 double bond was left intact. After protection of the primary alcohol with a trityl group (**24a**), the secondary OH of **24a** was converted to a MsO group and selective cleavage of the TBS vs TBDPS ether with TBAF directly gave **2a**, as the result of a one-pot cyclization.

A significant NOE between H12 and H15 indicated a *cis*-arrangement. Additional correlation data (COSY and NOESY) for H13, H14, H15, and H27 confirmed the relative configuration of all stereocenters.

Alternatively, the primary hydroxy group at C27 could be quantitatively converted into a selenoaryl ether (with 2-nitrophenylselenyl cyanide and Bu_3P)[17] or, more quickly and without requiring any chromatographic separation, into its 2-pyridylselenyl ether (**24b**) with di-2-pyridyl diselenide and trimethylphosphine ($PySeSePy/Me_3P$).[18]

Activation of the C15 hydroxy group of **24b** as its Ms derivative, followed by removal of its TBS group, as above, gave directly the tetrahydrofuran derivative **2b** in 95% yield. The deprotection and cyclization steps could be easily followed by TLC, as the three spots were clearly distinguished.

Compound **2b** was characterized by NMR, as well as by its strong $[M + H]^+$ and $[M + Na]^+$ peaks in the FABMS (in sharp contrast to other analogues of type **2**, the corresponding peaks of which could hardly be detected). Independent experiments with other selenopyridyl ethers and with **2b** (to be reported elsewhere) showed that their oxidation with hydrogen peroxide or other peroxo derivatives afforded the desired double bond (to be introduced between C14 and C27 in a later stage of the total synthesis of **1**).

In summary, completion of the total synthesis of **1** seems really feasible soon, as a route to the main fragment (C9−C22, **2a**/**2b**) has now been disclosed and key steps have been optimized. The generation of titanium enolates without cleavage of PMB and/or TBS ether functionality, the excellent yields of the boron-mediated aldol reactions after appropriate workup, and the use of $PySeSePy/PMe_3$ are all worthy of noting. In the future different stereoisomers of the C9−C22 building block will be combined with the C1−C5 stereoisomers already reported,[3] to obtain a set of diastereomers and analogues of (−)-amphidinolide K, without major deviations from the original strategy.

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Supporting Information Available: Experimental procedures and characterization data for the main compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, 307. (b) Evans, D. A.; Cage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. (c) $LiBEt_3H$ ("Superhydride", 2.2 equiv) in THF at −78 °C cleaved exclusively the chiral auxiliary of **11**; however, in the case of **23**, several products were produced.

(17) (a) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697. (c) Sayama, S.; Onami, T. *Tetrahedron Lett.* **2000**, *41*, 5557.

(18) (a) Martín, M.; Martínez, G.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2004**, *45*, 5559. (b) Esteban, J.; Costa, A. M.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2004**, *45*, 5563. For the use of the PySe group in *syn* selenoxide eliminations, see: (c) Toshimitsu, A.; Owada, H.; Terao, K.; Uemura, S.; Okana, M. *J. Org. Chem.* **1984**, *49*, 3796. (d) Toshimitsu, A.; Hayashi, G.; Terao, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2113 and references therein.