A Streamlined Synthetic Approach to SPMs

Nicholas Wourms, Alisa Litvintsev, Jodi C. Westcott, and David Fichtner

Cayman Chemical Company, Ann Arbor, MI

KEY FINDING

Structural similarities in SPMs can be harnessed to create scalable, chirally pure, and customizable derivatives

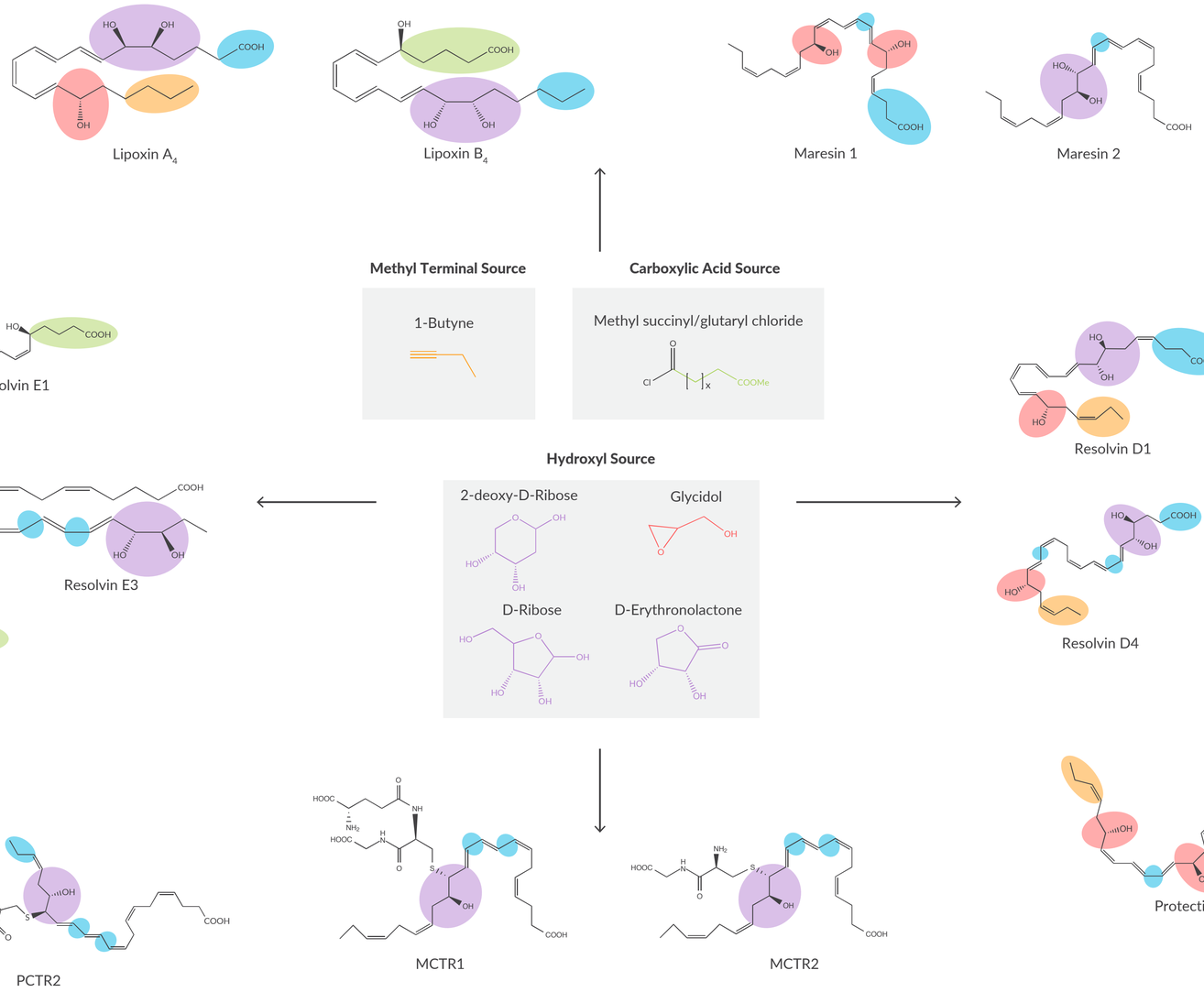

FIGURE 1

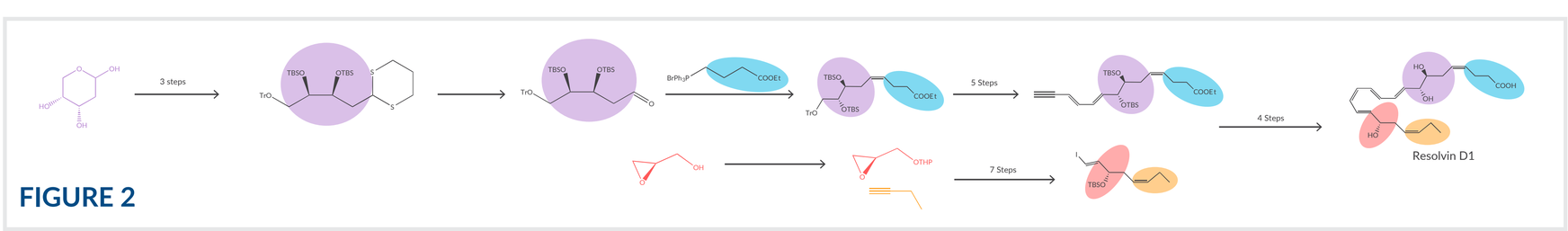

FIGURE 2

2-deoxy-D-Ribose

- Inexpensive and readily available from multiple vendors, which permits scalability
- Provides preferred *syn* diol required for SPM synthesis
- Enantiomerically pure, avoiding any enrichments or difficult purifications
- Allows for bilateral carbon-carbon coupling
- Allows for selective protections of the hydroxyl groups
- Payne rearrangement can be utilized to form internal and external epoxides
- Lactol can be forced open to the aldehyde to improve reactivity
- For resolvin D4 and resolvin E3, D-erythronolactone and D-ribose, respectively, are used in lieu of 2-deoxy-D-ribose for the diol source[4]

Glycidol

- Commercially available in both enantiomerically enriched forms from multiple vendors
- Fairly inexpensive, permitting scalability
- Desired stereochemistry set early in synthesis
- Allows for bilateral carbon-carbon coupling
- Protection of primary alcohol allows for opening the epoxide with a nucleophilic attack
- Substitution of the glycidol enantiomer provides the aspirin-triggered epimer by the same synthetic path as the parent SPM

Common Commercially Available Synthons

- [3-(Ethoxycarbonyl)propyl]triphenylphosphonium bromide
- Propyltriphenylphosphonium bromide
- (Formylmethyl)triphenylphosphonium chloride
- Methyl (triphenylphosphoranylidene)acetate

1-Butyne

- 1-Butyne and 1-butyne-d_5 are commercially available
- Useful in completing ω-chain *via* organolithium addition to the THP-glycidyl
- 1-Butyne-d_5 is an efficient way to radiolabel most of the D-class resolvins
- 1-Butyne-d_5 is isotopically enriched, affording a d_0 value of less than 1%

Methyl succinyl chloride/Methyl glutaryl chloride

- Commercially available, inexpensive
- Useful in the synthesis of 4/5-carbon hydroxy acid systems in many SPMs
- Ketoalkyne can be formed through Friedel-Crafts acylation
- Midland reduction of the ketone affords desired stereochemistry of hydroxyl group
- (S)-Alpine-Borane® is commercially available for use in Midland reduction

DOWNLOAD A COPY OF THIS POSTER

SPM SYNTHETIC STRATEGIES: AN EXAMPLE WITH RESOLVIN D1

Specialized pro-resolving lipid mediators (SPMs) are a class of compounds that are biosynthesized from polyunsaturated fatty acids (PUFAs) and exhibit pro-resolving capabilities. Although the subset lipoxins were initially discovered nearly 40 years ago, the role of SPMs in the progression and resolution of inflammation is still being explored and new SPMs are being discovered to this day.[1,2]

Structural similarities in SPMs can be exploited to create a scalable and streamlined synthetic approach to multiple derivatives. Researchers have synthesized over 20 SPMs from just a few commercially available starting materials. With these building blocks, a major portion of any SPMs and their derivatives can be synthesized. Five of these integral pieces and their useful synthetic qualities are outlined (**Figure 1**).

Resolvin D1 (RvD1) is one of many DHA-derived SPMs. RvD1 synthesis utilizes three of the building blocks in **Figure 1**. Both 2-deoxy-D-ribose and enantiomerically enriched glycidol afford fixed stereochemistry of the hydroxyl groups.[1] Hence, RvD1 can be synthesized in higher yields and larger quantities than if an enantiomerically impure reagent was used. Incorporating 1-butyne not only completes the ω-chain but offers easy radiolabeling.

Additional detail on the three synthons and their specific role pertaining to RvD1 are shown (**Figure 2**).

Current literature details the synthesis of RvD1 using 2-deoxy-D-ribose and (R)-glycidol.[1,3] Using this chiral pool approach, RvD1 can be synthesized with the hydroxyl groups enantiomerically set at the beginning of the synthesis.

2-deoxy-D-Ribose is a key component in the synthesis of RvD1. In some papers, the acetonide-protected lactol of 2-deoxy-D-ribose is utilized to build RvD1.[3] This establishes chirally pure hydroxyl groups early in synthesis and offers the ability for addition on either side of the synthon. Leveraging naturally chirally pure compounds in this synthesis avoids messy purifications or uncertainties.

The monohydroxyl group in RvD1 is also pre-set at the beginning of synthesis by using (R)-glycidol. Glycidol is commercially available in both enantiomerically enriched forms, giving flexibility to make both RvD1 and aspirin-triggered RvD1. The glycidol is THP-protected before opening the epoxide by organolithium addition of 1-butyne.[1] The addition and subsequent reduction of the 1-butyne completes the ω-chain. Commercially available 1-butyne-d_5 can be utilized for radiolabeling RvD1. The Rodriguez and Spur paper detailing the synthesis of RvD1 offers an alternative method for radiolabeling through Boland reduction of the 13(Z) olefin late in the synthesis.[3] However, even with fresh deuterated solvents, this way of radiolabeling can be difficult to monitor and is susceptible to exchange.

The innate properties of these three low-cost and widely available synthons make a scalable and streamlined synthesis for RvD1 feasible. These strategies are applicable to the synthesis of other resolvins.

Manipulating these same building blocks and others (Figure 1) allows for the synthesis of existing and future SPMs.

References

1. Serhan, C.N., Hamberg, M., and Samuelsson, B. *Biochem. Biophys. Res. Commun.* **118(3)**, 943-949 (1984).
2. Serhan, C.N. and Petasis, N.A. *Chem. Rev.* **111(10)**, 5922-5943 (2011).
3. Rodriguez, A.R. and Spur, B.W. *Tetrahedron Lett.* **53(51)**, 6990–6994 (2012).
4. Nagarapu, L., Karnakanti, S., and Bantu, R., *Tetrahedron* **68(29)**, 5829-5832 (2012).